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REVIEW ARTICLE

Congenital Zika syndrome

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Abstract

In February 2016, the World Health Organization declared Zika virus (ZIKV) infection a public health emergency of international concern because it caused congenital Zika syndrome (CZS). The CZS is considered a specific pattern of birth defects caused by ZIKV infection, which is transmitted by the bite of the Aedes aegypti *mosquito. The CZS clinical manifestations are broad and nonspecific, including microcephaly, subcortical calcifications, ocular alterations, congenital contractures, early hypertonia, and pyramidal as well as extrapyramidal symptoms. The ZIKV has gained great importance because it has affected a large percentage of the population worldwide during the last few years, despite the measures implemented by international organizations. The pathophysiology and non-vectorial transmission routes of the virus are still under study. The diagnosis is made upon suspicion of ZIKV infection, the patient's clinical manifestations, and it is confirmed by molecular laboratory tests demonstrating the presence of viral particles. Unfortunately, there is no specific treatment or vaccine for this condition; however, patients receive multidisciplinary care and constant monitoring. Therefore, the strategies that have been implemented are directed toward preventive measures and vector control.*

Keywords: *Zika virus. Congenital Zika syndrome. Microcephaly.*

Síndrome congénito por virus Zika

Resumen

En febrero de 2016, la Organización Mundial de la Salud declaró a la infección por virus Zika una emergencia de salud pública de importancia internacional por ser la causa del síndrome congénito por virus Zika. Este síndrome es considerado un patrón específico de defectos al nacimiento causados por la infección por virus Zika, que se transmite por la picadura del mosquito vector Aedes aegypti *y cuyas manifestaciones clínicas son amplias e inespecíficas, entre las que destacan microcefalia, calcificaciones subcorticales, alteraciones oculares, contracturas congénitas, hipertonía temprana y síntomas de afectación piramidal y extrapiramidal. Este virus ha tomado gran importancia debido a que durante los últimos años ha afectado a un gran porcentaje de la población en todo el mundo, a pesar de las medidas implementadas por organizaciones internacionales. La fisiopatología y las vías de transmisión no vectorial de la infección aún siguen en estudio. El diagnóstico se realiza ante la sospecha por las manifestaciones clínicas del paciente, y se confirma mediante pruebas moleculares de laboratorio en las que se demuestre la presencia de partículas virales. Desafortunadamente, no existe aún un tratamiento ni una vacuna específica para*

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este padecimiento; sin embargo, los pacientes reciben cuidados multidisciplinarios y monitorización constante. Las estrategias que se han implementado se dirigen hacia medidas preventivas de la infección y el control de los vectores.

Palabras clave: *Virus Zika. Síndrome congénito por virus Zika. Microcefalia.*

Introduction

Congenital Zika syndrome (CZS) is considered a specific pattern of newborn defects caused by Zika virus (ZIKV) infection, a microorganism that has been considered a teratogenic agent[1-3]. Although the pathophysiological pathways by which this infection causes organ dysfunction are still under investigation, nervous system, musculoskeletal and visual impairment have been described in infected newborns. The following clinical manifestations stand out: microcephaly with subcortical calcifications, retinal alterations, congenital contractures, early hypertonia, and extrapyramidal symptoms, which can occur together or separately in each patient[4,5].

ZIKV infection has become very important in recent years because it is associated with significant health problems worldwide and has been classified as a public health emergency of international concern[6]. This has prompted various international organizations such as the World Health Organization (WHO), the United States Centers for Disease Control and Prevention (CDC), and the Pan American Health Organization (PAHO) to take preventive measures to avoid its further progression as a pathological entity[6-8].

In October 2015, the *Secretaría Estatal de Salud* (State Health Secretariat) of Pernambuco, Brazil, reported 26 cases of microcephaly associated with ZIKV infection[8,9]. Subsequently, countries worldwide began to report cases of patients with microcephaly and infection with serum ZIKV viral load. ZIKV infection during pregnancy was found to cause CZS and complications during pregnancy, such as preterm labor or even spontaneous abortion[5,10].

In Mexico, epidemiological surveillance has been conducted through the *Secretaría de Prevención y Promoción a la Salud* (Secretariat of Prevention and Health Promotion). According to the information bulletin "Confirmed cases of ZIKV disease" for the 52nd epidemiological week of 2021, 12,991 cases of ZIKV infection were reported from 2015 to December 31, 2021, with Veracruz, Yucatán, and Nuevo León being the states with the highest number of confirmed cases. In addition, it was reported that 7152 pregnant patients presented ZIKV infection, with Yucatán having the highest number of cases with 926, followed by Veracruz with 888 cases and Tamaulipas with 692 cases[11]. In addition, 44 cases confirmed by epidemiological association of CZS and 56 laboratory-confirmed cases of CZS were reported[12,13].

At present, the diagnosis of ZIKV disease in first-contact health services is complicated due to the similarity of the clinical picture with diseases caused by other viruses of the same genus, such as Dengue and Chikungunya virus[14-16] (Table 1). Symptoms are generally mild, lasting 2-7 days, and may consist of fever, rash, conjunctivitis, muscle and joint pain, malaise, and headache; however, most infected patients are asymptomatic[8].

ZIKV

The virus was named after the Zika forest in Entebbe, Uganda, Africa, where it was discovered in 1947 in rhesus monkeys, in which transmission was only enzootic, restricted to primate-mosquito circulation[17,18].

Subsequently, the first case of human transmission was reported in 1954 in a 10-year-old Nigerian girl who had a serum viral load of ZIKV. However, it was difficult to relate her clinical presentation to ZIKV infection because parasites of the genus *Plasmodium* were also found in her blood samples[19]. In the same year, two more cases of ZIKV infection in humans were reported, confirmed by increased serum-neutralizing antibodies[20]. In 1966, ZIKV infection was massively detected in the Asian population, which increased research on human transmission. As a result, the ability of the virus to infect humans through a vector was reported, and its wide geographical distribution and the presence of different viral lineages, both from the African and Asian continents, were demonstrated[21]. Subsequent studies showed that ZIKV is an arbovirus of the genus *Flavivirus*, whose main vector is the *Aedes aegypti* mosquito[1]. Since then, cases of ZIKV infections in humans with diverse clinical manifestations have been reported; over time, cases with more severe alterations have appeared[5,15,22].

Subsequently, a high incidence of cases was reported in 2007 on the islands of Yap in Micronesia[23], and in 2008 the first cases of sexual transmission were reported[24]. In 2013 and 2014 in French Polynesia, the first cases of ZIKV infection were reported with

Table 1. Main clinical manifestations in Zika, dengue and Chikungunya virus infections

Signs and symptoms	Zika	Dengue	Chikungunya
Reason for consultation	Exantema o prurito	Fever, myalgia	Joint pain, fever
Fever	Mild	Moderate	Intense
	Very infrequent	Very frequent	Very frequent
	Duration: 1-3 days	Duration: 5-7 days	Duration: 5-7 days
Exanthema and features	Typically from day 1	Appears from 5th to 7th day	Appears on the 2nd or 3rd day
	Maculopapular, cephalo-caudal	Not characteristic	Not characteristic
Pruritus	Moderate to intense	Mild to severe	Mild to moderate
Conjuntivitis	Very frequent	Infrequent	Adults: Very rare/Children: Very common
Neurological manifestations	Possible and serious	Infrequent	Infrequent (can be frequent and severe in newborns)
Headache	Mild to moderate	Intense and frequent	Mild to moderate
Retro-orbital pain	Infrequent	Intense and frequent	Infrequent
Polyarthralgia	Frequent	Absent	Very frequent
Polyarthritis	Frequent	Absent	Frequent
Myalgia	Infrequent	Very frequent and intense	Frequent, moderate to severe
Diarrhea	Very infrequent	Frequent	Very infrequent
Skin bleeding	Very infrequent	Frequent	Very infrequent
Mucosal bleeding	Very infrequent	Alarm sign	Very infrequent (severe when present)

post-infectious onset of Guillain-Barré syndrome, maternal-fetal transmission, and the presence of viral load in semen samples from asymptomatic donors[25]. In the Americas, it is estimated that ZIKV was introduced between May and December 2013; however, the first reported cases of CZS were in May 2015 in Brazil, attributed to globalization and migratory movements due to social and sporting events[5,26,27].

The worldwide spread of the virus was rapidly progressive, and cases began to be documented in subtropical areas, Central and North America, and 87 countries of different geographic distribution. More than 500,000 cases were reported worldwide. This prompted the WHO to declare ZIKV infection as a Public Health Emergency of International Concern on February 1, 2016, and temporarily confirmed the association of ZIKV infection with microcephaly, Guillain-Barré syndrome, sexual, blood and vertical transmission, as well as the occurrence of severe birth defects in neonates with parents with a history of ZIKV infection[5-7,20].

ZIKV belongs to the *Flavivirus* genus of the *Flaviviridae* family and measures approximately 40 nanometers (nm) in diameter. Its genetic material corresponds to a single-stranded ribonucleic acid chain (single-stranded RNA) of positive polarity, which encodes a polyprotein whose translation gives rise to three structural proteins: capsid protein (C), membrane precursor (prM) and envelope protein (E), and 7 non-structural proteins (NS): NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5[28]. The function of each of these is described in Table 2.

The viral particle consists of a symmetric icosahedral structure with a viral envelope containing the E and M proteins as molecules for attachment and host cell recognition (Fig. 1A)[26,29]. The entry of ZIKV into the host cell is mediated by the E protein, which allows attachment and fusion to the specific receptors TIM1, TYRO-3, and AXL, thus activating the endocytosis processes and the entry of the virion into the cell cytoplasm[29,30].

Inside the cell, non-structural proteins bind to the endoplasmic reticulum (ER), forming a complex that allows replication and assembly of viral RNA called viroplasm[31]. This involves NS4A and the formation of ER invaginations in which NS1 subsequently acts to initiate the viral genome replication processes, and NS3 RNA helicase and NS5 polymerase act, assisted

Table 2. Functions of Zika virus proteins

Type	Protein	Function
Structural	Protein C	Forms the viral capsid
	Protein E	Enables membrane binding and fusion with the host cell, penetration and hemagglutination during the viral replication cycle
	Protein prM	Generates M protein, which releases mature virion out of the cell forming complexes with E protein
Non-structural	NS1	Initiates the process of viral RNA genome synthesis
	NS2A	Interacts with NS3 and NS5 for viral packaging and replication
	NS2B	Interacts with NS3 for viral packaging and replication
	NS3	Harbors RNA protease and helicase activity, essential for viral replication and survival
	NS4A	Participates in the localization of the replication complex to the membrane
	NS4B	Assists NS3 protein
	NS5	Participates in the inhibition of the host innate immune system and is a coadjuvant of the NS3 protein in the nuclear localization of the virus

Adapted from Panwar[28].

by NS4B. Viral packaging requires the action of NS2A and NS2B through viral RNA packaging vesicles. In these vesicles, the structural proteins are integrated, a process necessary for their transport into the cell, mainly through the interaction of the E protein and prM with the Golgi apparatus[28,31,32]. At the same time, ZIKV generates modifications in centrosomes to reorganize microtubules and facilitate their transport and intracellular propagation[33,34]. Subsequently, for viral release into the extracellular environment, it was described that ZIKV can induce a process of apoptosis mediated by autophagy, processes of degranulation of viral RNA packaging vesicles, or processes of exocytosis[34]. The NS5 viral protein antagonizes the type I interferon response to favor viral dissemination. This leads to proteasomal degradation of STAT2 (a transcription factor that generates chain responses of the immune system), allowing ZIKV to infiltrate the lymphatic and circulatory system, which leads to the dissemination of the virus throughout the body and the development of clinical manifestations (Fig. 1B)[30,35].

ZIKV transmission can be vector-borne or non-vector-borne[1]. Vector-borne transmission occurs when the virus infects the host through mosquito bites[36]. This explains the sylvatic transmission cycle, where non-human primates and endemic mosquitoes (enzootic vectors) are involved, as well as human-mosquito-human transmission in urban and suburban regions[1,37]. On the other hand, the mechanisms of non-vectorial infection that has been described are sexual[38], vertical[39], perinatal[40], blood transfusion, and organ transplantation[41], as well as contact with body secretions such as tears, saliva, urine, or sweat[42].

Vertical, maternal-fetal transmission of Flaviviruses is unusual. It has been proposed that these viruses follow different pathways that vary according to gestational age and the route of maternal infection (vectorial or non-vectorial) to invade and replicate viral proteins in fetal tissue[43,44].

Pathophysiology

ZIKV has a strong tropism to ectodermal derivatives, which confers greater dissemination potential with a wide variety of clinical manifestations and specific alterations according to the infected tissue[35,45]. It has been reported that ZIKV presents neuronal tropism and towards other organs, such as the liver, kidney, heart, spleen, testicle, and ovary since viral RNA has been found in these tissues[30,46,47].

ZIKV tropism is mediated by type I and III interferon-stimulated genes, which induce signaling for the production of membrane proteins AXL and Tyro-3, members of the receptor tyrosine kinase-like protein family, which are expressed mainly in neuronal progenitor cells and play an important role in embryonic developmental homeostasis. In addition, the TIM1 glycoprotein, which interacts with ZIKV, has been found in multiple target organs, such as Hofbauer cells or placental macrophages, endothelium, and cytotrophoblast[30,47].

Moreover, detection of ZIKV RNA in fetal tissues has also been reported in the umbilical cord, placental cells such as macrophages, amniotic fluid, and brain, as well as in tissues from spontaneous abortions of first and second-trimester human fetuses, mainly in placenta and brain[8,30,47]. *In vitro* studies suggest that viral replication occurs mainly in Hofbauer cells, trophoblast cells, and fetal endothelium[48-50].

Vertical transmission of ZIKV can develop through the interaction of the virus in maternal blood or uterine

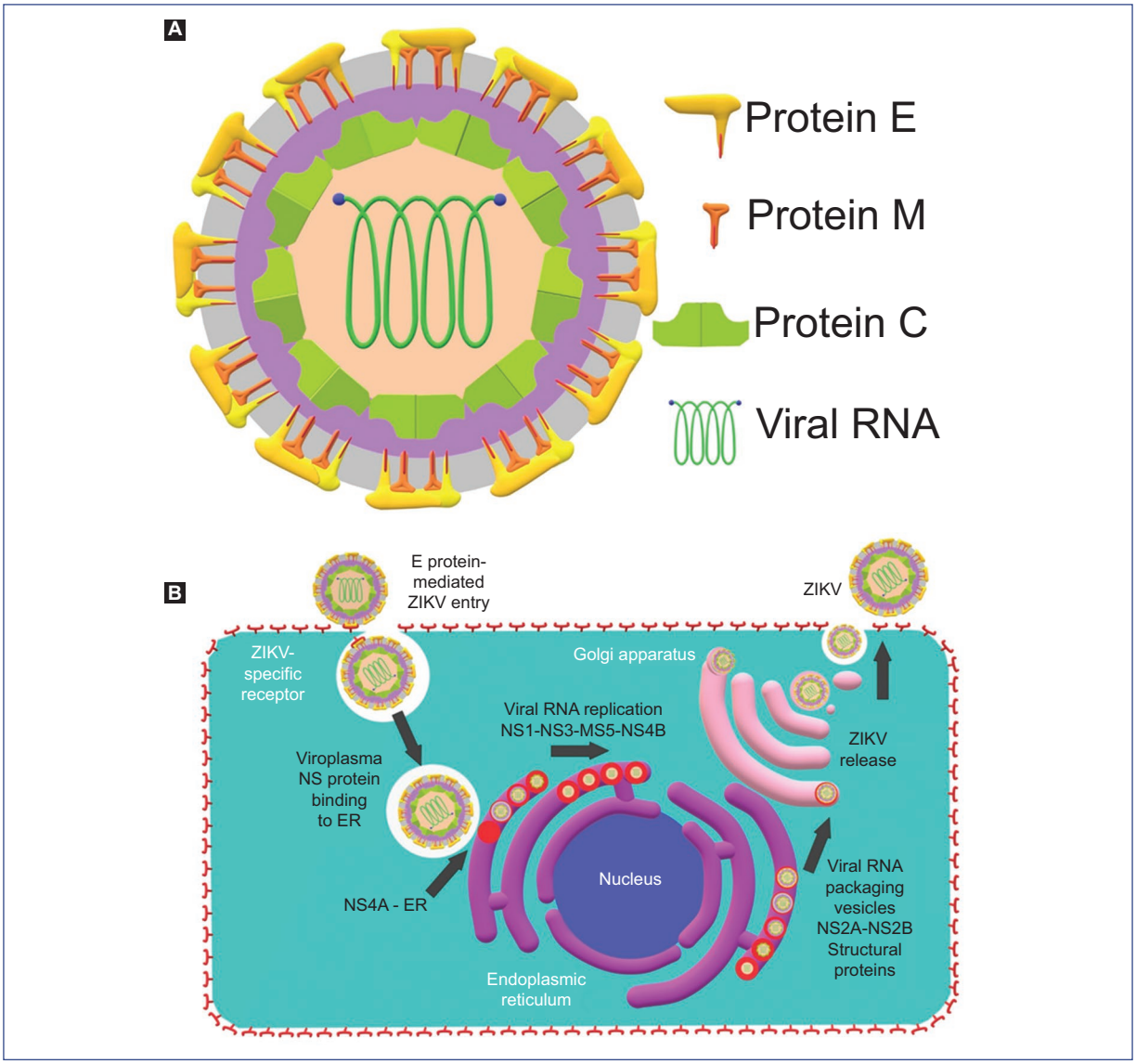

Figure 1. Zika virus. **A:** structure. **B:** viral cycle.

fibroblasts with embryonic cells[35,51]. For this, two hypotheses are considered: direct transfer or placental mediated response on placental precursor tissue such as trophoblast, chorioamniotic villi and membranes, Hofbauer cells, umbilical cord endothelial cells, and amniotic epithelial cells[44,50-52]. The direct transfer theory stipulates that viral contact occurs within the first 10 weeks of gestation through the presence of ZIKV in maternal blood or uterine fibroblasts, thus infecting embryonic precursor cells of neuronal tissue due to its neurotropism. On the other hand, the theory of placental response can be considered complementary to the pathophysiology since the inflammatory response caused by ZIKV infection produces a disruption of placental signals that mediate neuronal development and changes the profile of inflammatory markers in fetal organs, which eventually generates the clinical manifestations depending on the specific tissue affected[49,52-54].

According to the CDC, approximately 5% of pregnant patients with maternal ZIKV infection either lose the pregnancy or develop birth defects[50,51]. Gestational age and host genetic variation are important determinants of placental infection and immune system function[35]. In addition, infection acquired during the first trimester increases the risk of developing CZS in the embryo[51,55]. Statistically, infection in the first two trimesters is associated with severe alterations in target organs such as the brain, eye, and male and female genital tract;

however, infection in any trimester of pregnancy is associated with adverse fetal outcomes[35,55-57].

During the 3rd week of embryonic development, gastrulation and, thus, organogenesis begins. The external epithelium of the body and the neural tube are formed from the ectoderm. The external body epithelium gives rise to organs and structures that are in contact with the outside world (e.g., sensory epithelium of the ear, nose, and eye, epidermis, skin, nails, mammary, sweat, and sebaceous glands), anterior pituitary, and tooth enamel. At the same time, from the neural tube, the components of the nervous system are formed from the neural plate (notochord-induced thickening of the ectoderm) and neural crest cells (NCC) (Fig. 2)[58,59].

NCCs undergo an epithelial-mesenchymal transition for their active movement and migration into the mesoderm[50], directed by the expression of the bone morphogenetic protein, WNT signaling pathways, and by fibroblast stimulating factor 8 expressed by the mesoderm. In addition, they are regulated by the expression of cell adhesion molecules and extracellular matrix molecules (fibronectin, laminin, and type IV collagen), filopodia, guidance molecules (neuropilin/semaphorin), and by planar cell polarity. It should be noted that NCCs can be differentiated by prior programming and by interaction with nearby tissues[59]. NCCs are divided into three regions for their study: cranial, circumpharyngeal, and truncal, each with specific derivatives according to its region[59]. NCCs contribute to the formation of the peripheral nervous system, meninges, melanocytes, odontoblasts, medullary chromaffin cells, and a large part of the connective tissues that form the cervical and craniofacial territory, including bone, cartilage, and muscle tissue[60]. This is why an agent with ectodermal tropism can present diverse clinical manifestations[61].

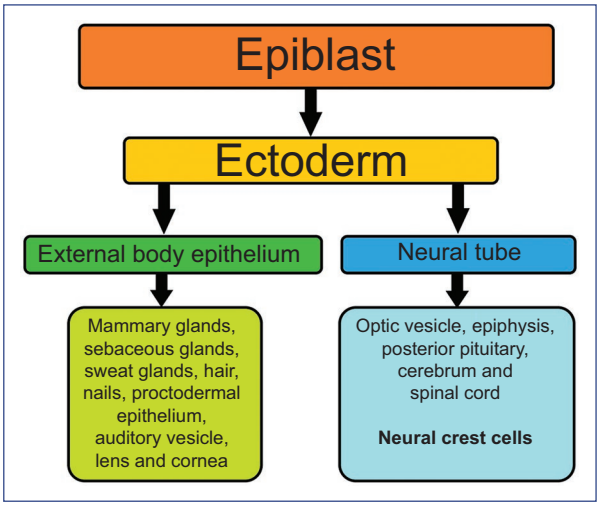

Figure 2. Ectodermal germinal layer derivatives.

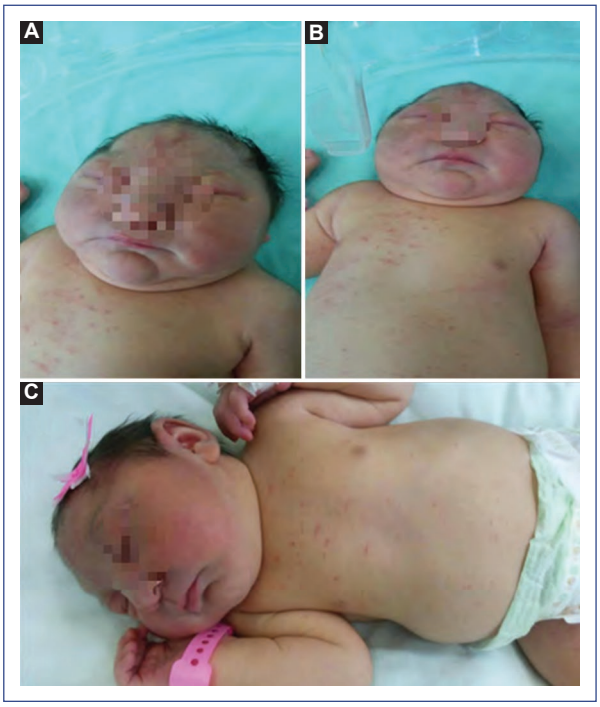

Figure 3. Newborn with clinical features of microcephaly. Female patient at 39 weeks of gestation. **A** and **B:** frontal view. **C:** lateral view. Image obtained from Aviña-Padilla et al.[64].

Clinical, embryonic, and fetal manifestations of CZS

The clinical features of CZS are a consequence of direct neurological involvement and intracranial volume loss, causing structural, and functional alterations[4,62,63]. Structural alterations include cranial morphology, cerebral and ocular anomalies, congenital contractures, and mainly microcephaly (Fig. 3A-C)[64], while functional alterations are exclusively related to neurological impairment[55,65,66].

Chronic cerebral neuropathy in ZIKV-infected children consists of intracranial calcifications, typically subcortical (Fig. 4A and B), increased fluid spaces (ventricular and extra-axial) (Fig. 4C and D), cortical thinning with abnormalities in the convolutions (polymicrogyria, pachygyria, and agyria), hypoplasia or absence of the corpus callosum, decreased myelin, and hypoplasia of the cerebellum or cerebellar vermis[67-69].

Calcifications have also been identified in the basal ganglia and brainstem. Ultrasound or magnetic

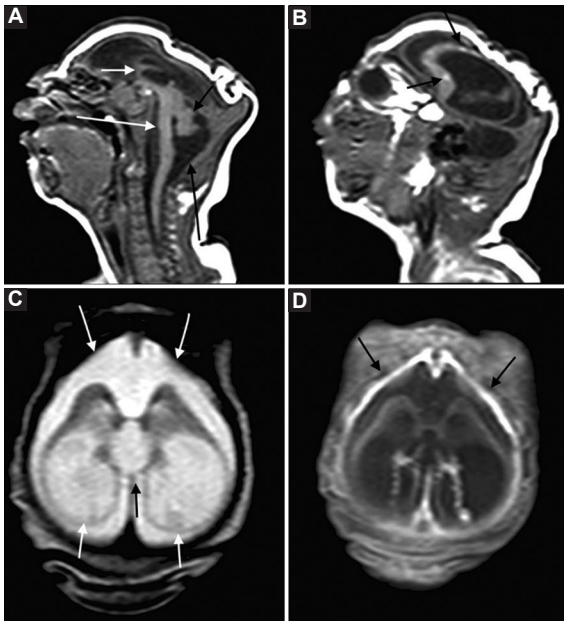

Figure 4. CT scan of newborn with severe microcephaly. **A:** profound craniofacial disproportion, corpus callosum (short white arrow), brainstem (long white arrow) and cerebellar hypoplasia (short black arrow), enlarged cisterna magna (long black arrow). **B:** calcifications in frontal lobe. **C:** severe ventriculomegaly. **D:** increased thickness of pachymeninges. Image obtained from de Fatima Vasco Aragao et al.[68].

resonance imaging (MRI) studies can detect these brain abnormalities during the prenatal period. In cases of microcephaly, damage of the central nervous system caused by ZIKV occurs by direct and indirect cellular injury through various pathways such as apoptosis, regulation of the immune response, ubiquitination, and viral replication, mostly in neuronal progenitor cells[35,70]. This apoptotic capacity may explain the alterations in the embryonic neurodevelopment of infected products. In addition, experiments have been reported in animal models, where infection in postnatal products causes dysfunction of cell death pathways, decreased proliferation of stem cells in the periventricular zone, and disruption of corticospinal pyramidal neurons[71,72]. These are not the only factors contributing to microcephaly caused by ZIKV; NCCs are also affected by this virus. Consequently, they produce pro-inflammatory cytokines that induce apoptosis via the paracrine pathway affecting neuronal progenitor cells[35].

Neurological alterations caused by ZIKV infection include hypertonia, hypotonia, spasticity, hyperreflexia, severe irritability, and seizures. Some patients with confirmed or probable infection present fetal disruption sequence phenotype, characterized by severe microcephaly, marked craniofacial disproportion, occipital bone prominence, altered hair implantation, short neck, redundant nuchal and cranial folds, retrognathia, contractures, and multiple arthrogryposes[73,74].

In the eyes, viral RNA has been detected in the cornea, optic nerve, and neurosensory retina. The most frequent ocular structural anomalies are, in particular, microphthalmia, coloboma, congenital cataracts, and intraocular calcifications. Likewise, cases of chorioretinal atrophy and retinitis pigmentosa have been reported, generally affecting the macular region and producing atrophy of the optic nerve[75].

In the male reproductive tract, the infection damages spermatogonia and Sertoli cells, destroys testicular architecture, decreases sperm motility, and thus reduces fertility[76]. In parallel, in the female genital tract, viral RNA has been reported in the cervical mucosa up to 11 days after the onset of symptoms. *In vitro* studies showed that uterine fibroblasts have increased susceptibility to ZIKV, contributing to fetal developmental damage[35,77].

On the other hand, congenital contractures of one or multiple joints (arthrogryposis multiplex congenita) have been described in fetuses and newborns with congenital ZIKV infection. The clinical picture of congenital contractures varies according to proximal or distal location, laterality, upper or lower limb, and severity, as reflected by neurological damage[78,79].

Neurogenic factors affecting the corticospinal tract and motor neurons or their interactions may cause fetal motor abnormalities, resulting in decreased movements and contractures. However, the specific mechanism causing contractures in prenatal ZIKV infection is not yet fully understood[80].

To date, the means of non-vectorial transmission and the pathophysiology at the molecular level of this condition are still under investigation.

Diagnosis

Due to the severe effects caused by ZIKV infection on embryonic and fetal development, it is necessary to identify risk factors and make a timely diagnosis. As has been described, CZS can present diverse clinical manifestations, both mild and severe; in addition, the clinical data presented are nonspecific since different infections can also cause them during pregnancy[81]. Therefore, it is important to detect pregnant patients

with probable ZIKV infection through adequate prenatal screening, where all pregnant women should be evaluated to identify possible risk factors[82].

Risk factors for ZIKV exposure include[81-84]:

– Living in or having visited areas with active ZIKV transmission in the past 15 days or during pregnancy.
– Having had unprotected sex in the 2 weeks before conception with a partner who has traveled or lived in areas with active virus transmission in the previous 6 months, regardless of whether or not symptomatology was present.

The clinical presentation of CZS is generally characterized by disruption in brain development, both embryonically and at the fetal level[20,85], characterized by direct neurological disturbance followed by the collapse of the fetal cranial vault due to decreased intracranial hydrostatic pressure[4,62,63].

For its study and diagnosis, PAHO has typified CZS under the following criteria[86]:

A case of congenital syndrome suspected to be associated with ZIKV infection is determined when the live newborn presents:

– Microcephaly, whose occipitofrontal head circumference measurement is below the third percentile according to standard growth charts for age, sex, and gestational age at 24 h after birth.
– Maternal history of residence or travel to an area with circulation or suspected circulation of ZIKV.
– Unprotected sex with a partner with a history of residence or travel to an area with ZIKV circulation or suspected ZIKV circulation.

A case of congenital syndrome probably associated with ZIKV infection is determined when the live newborn meets the criteria for a case of congenital syndrome suspected to be associated with ZIKV infection and with any of the following features:

– Intracranial morphological alterations diagnosed by any imaging method, excluding other known possible causes.
– Maternal history of having presented with exanthema during pregnancy.

A case of congenital syndrome confirmed to be associated with ZIKV infection:

– When the live newborn of any gestational age meets the criteria for a case of congenital syndrome suspected of being associated with ZIKV infection and in whom ZIKV infection has been laboratory confirmed, regardless of the detection of other agents.

Infection by vertical transmission can occur in any trimester of pregnancy, regardless of whether the mother has symptoms or not[20,55,59,60]. However, not all products exposed to ZIKV become affected. It is estimated that 70-80% of exposed products do not present alterations suggestive of ZIKV infection. Of the 20-30% who become infected, only 5-14% develop CZS. On the other hand, about 4-7% culminate in fetal loss; the rest are asymptomatic[20].

The general malformations associated with CZS are[81]:

– Severe microcephaly, where the skull has partially collapsed.
– Decreased brain tissue with calcifications in the subcortical region.
– Damage of the fundus, manifesting with macular scarring and focal retinal pigmentary staining.
– Congenital contractures such as clubfoot (talipes) or arthrogryposis.
– Congenital hypertonia limiting body movement shortly after birth.

It should be noted that microcephaly caused by ZIKV is diagnosed under the following parameters[81]:

Defined dongenital microcephaly:

– For live births:
  • Occipitofrontal circumference at birth less than the 3rd percentile for gestational age and sex within the first 2 weeks of life.
– For stillbirths and elective terminations
  • Occipitofrontal circumference at birth less than the 3rd percentile for gestational age and sex.

Possible congenital microcephaly

  – For live births
  • Occipitofrontal circumference less than the 3rd percentile for age and sex after 6 weeks of age.
  – For all pregnancy outcomes
  • Microcephaly diagnosed or suspected by prenatal ultrasound in the absence of available postnatal occipitofrontal circumference measurements.

The imaging methods for CZS diagnosis are ultrasonography (USG), computed tomography (CT), and MRI[87]. It is important to remember that during pregnancy, ultrasounds should be performed every trimester for fetal and maternal risk screening during prenatal control visits. Likewise, during the intrauterine stage, it is also advisable to use USG and MRI; while in the extrauterine stage, CT can be performed[82,88].

Cranial alterations such as microcephaly and intracranial calcifications can be identified mainly at the end of the second and beginning of the third trimester[89]. On the other hand, images taken by CT or MRI can identify some of the findings that have been described in patients with CZS, such as intracranial calcifications, ventriculomegaly,

increased extra-axial fluid, polymicrogyria (alterations of neuronal migrations resulting in excessive cortical folds and shallow sulci), reduction of brain parenchymal volume, cortical atrophy or malformation, hypoplasia of the cerebellum or cerebellar vermis, delayed myelination, and hypoplasia of the corpus callosum[40,89-91].

In addition, laboratory diagnosis of CZS should be made on clinical suspicion and identification of risk factors by molecular testing to confirm or rule out the presence of ZIKV, such as real-time polymerase chain reaction or time-dependent neutralization of antibodies (NNT), with blood samples from both the newborn and the mother, or embryonic annexes such as the umbilical cord or placenta, to prevent possible cases of CZS[92,93]. Detection of immunoglobulin (Ig)M antibodies is possible by enzyme-linked immunoadsorbent assay and immunofluorescence in cerebrospinal fluid samples or by amniocentesis[73,86,93]. IgM antibodies can be detected in serum from the 5th or 6th day after symptoms onset, and a positive serology requires a positive NNT test to confirm infection. For this purpose, it is important to strictly follow-up prenatal and postnatal control, both for the mother and the newborn[40,75].

Laboratory criteria for ZIKV infection in pregnant patients are as follows. For confirmed cases, virus isolation in a clinical specimen (blood/urine), nucleic acid detection in a clinical specimen (blood/urine), and detection of NNT in IgM-positive specimens. For probable cases, the presence of IgM antibodies, not confirmed by NNT in a serum sample, seroconversion of virus-specific IgG antibodies, or a four-fold increase in titer between samples taken in the acute and convalescent phase, the first serum is collected at the onset of the disease, and the second 10-14 days later. Furthermore, the detection of NNT in samples with negative IgM and positive IgG markers[73]. When congenital infection is suspected, it is advisable to perform laboratory tests to determine the presence of cytomegalovirus, herpes simplex, rubella, human immunodeficiency virus, toxoplasmosis, and syphilis infection to rule out other possible etiologies[54,69].

Treatment

Given the severe alterations caused by CZS, there is no specific treatment, and therapeutic measures are symptomatic, aimed at maintaining an adequate hydric status for the patient, as well as the use of analgesics and antipyretics. At present, some specific antiviral treatments and the development of anti-Zika vaccines are under study[20,35,73,94].

Patients with SCZ require constant monitoring, multidisciplinary care, referral to early intervention and stimulation centers, and family counseling[20]. Therefore, preventive measures are of major importance to avoid cases of CZS.

Preventive measures

According to PAHO and WHO, the best way to prevent the infection of communicable diseases is to control their vectors. Therefore, it is recommended to increase efforts to implement effective strategies to reduce vector density, mainly of the transmitting mosquito, which is widely distributed in the American continent, and the danger of exposure increases due to the emerging risk of population movement and migration[95].

In countries without local cases of ZIKV infection, it is recommended that patients with suspected ZIKV infection be tested for the virus to identify the circulating viral strains, the appropriate characterization of the outbreak, and the implementation of an adequate response. In countries with local cases of ZIKV infection, it is recommended to monitor the geographic spread of the virus to delimit the affected area, assess the clinical severity and public health impact, identify risk factors associated with ZIKV infection, and identify circulating ZIKV lineages. Any changes detected through surveillance should be promptly reported to the national prevention and control authorities to ensure that appropriate action is taken on time[73,95,96]. It is also necessary to take personal preventive measures, including wearing appropriate clothing (cotton and neutral colors) that covers most of the body (long-sleeved shirts, pants, socks, or caps, especially during peak mosquito activity hours). It is recommended to use mosquito nets on windows, doors, and at night, on the child's bed or crib. Furthermore, use mosquito repellents containing diethyltoluamide, picaridin, or icaridin according to the product manufacturer's instructions. In the house, look for and destroy possible sources of mosquito breeding sites by avoiding accumulations of stagnant water. For couples who wish to conceive, and either partner has traveled to high-risk areas, it is recommended that pregnancy be postponed for at least 8 weeks after the onset of symptoms or last possible exposure to the virus for women (symptomatic or not) or at least 6 months after the onset of symptoms or last possible exposure to the virus for men (symptomatic or not). Sexual partners of pregnant women returning from areas with local ZIKV transmission should maintain barrier-protected sex throughout pregnancy[95,96].

In conclusion, CZS is a pathological entity of wide distribution and easy transmission that can produce severe affectations. Its clinical presentation varies from asymptomatic to severe alterations that compromise the quality of life and even the course of life. The main neonatal clinical manifestations are microcephaly, ventriculomegaly, intracranial calcifications, ocular alterations, and congenital contractures. Its diagnosis is complex due to the variety of its clinical manifestations and its unspecificity; in addition, there is no specific treatment.

As health personnel, it is important to be constantly updated on this subject to identify risk factors, make a timely diagnosis and thus avoid both the effects during embryological development and the spread of this virus to more people in the population. Although there is no treatment or vaccine, personal prevention measures are straightforward and inexpensive, so it is essential to know them and promote them to avoid further complications. It is also important to continue with lines of research to better understand the pathogenic pathways through which it acts, optimize the diagnostic protocol, and produce specific therapeutic measures.

Ethical disclosures

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

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

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

Conflicts of interest

The authors declare that they have no conflicts of interest.

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SALUD Y HUMANIDADES

Educación y conocimiento liberador

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Resumen

Este ensayo inicia con un aforismo sobre la educación: «forjadora de las fuerzas liberadoras hacia el progreso de la condición humana», en su connotación espiritual, intelectual, moral y convivencial en armonía con el ecosistema planetario (progreso dignificante). Se realza la coincidencia de las mayores cotas históricas de educación profesional con la extrema degradación de la cultura occidental, reveladora del papel de la educación que favorece la pasividad ante el conocimiento y el orden imperante. Se contrastan los caracteres de la educación pasiva con los de la participativa basada en el desarrollo del pensamiento crítico. Se define el pensamiento crítico y se argumenta el tipo de ambiente educativo que lo estimula y encauza, en particular, el pensamiento complejo e integrador alusivo al sí mismo proyectado al quiénes somos y dónde estamos, ignorado por la ciencia reduccionista. Se especifican el conocimiento liberador y su finalidad: «entendernos como humanidad fraterna y encontrar nuestro lugar en armonía con el concierto infinitamente diverso del mundo viviente». Se sintetizan las revoluciones teóricas —hoy desestimadas—, simientes del conocimiento liberador que develaron al antropocentrismo y a los etnocentrismos como «prisiones del espíritu». Se concluye que el conocimiento liberador cumple el papel utópico de orientar y señalizar el caminar interminable hacia el progreso dignificante.

Palabras clave: *Conocimiento liberador. Colapso civilizatorio. Progreso dignificante. Pensamiento crítico. Educación participativa. Antropocentrismo.*

Education and liberating knowledge

Abstract

This essay begins with an aphorism on education: "forger of the liberating forces towards the progress of the human condition", in its spiritual, intellectual, moral and convivial connotation in harmony with the planetary ecosystem (dignifying progress). It highlights the coincidence of the highest historical levels of professional education with the extreme degradation of Western culture, which reveals the role of education that favors passivity in the face of knowledge and the prevailing order. The characteristics of passive education are contrasted with those of participatory education based on the development of critical thinking. Critical thinking is defined and the type of educational environment that stimulates and channels it is argued, in particular the complex and integrative thinking alluding to the self projected to who we are and where we are, absent in reductionist science. Liberating knowledge is specified and its purpose defined as "to understand ourselves as fraternal humanity and to find our place in harmony with the infinitely diverse concert of the living world". The theoretical revolutions —now dismissed— being seeds of liberating knowledge that revealed anthropocentrism and ethnocentrisms as "prisons of the spirit" are synthesized. It is concluded that liberating knowledge fulfills the utopian role of signaling the endless walking towards dignifying human progress.

Keywords: *Liberating knowledge. Civilizing collapse. Dignifying progress. Critical thinking. Participatory education. Anthropocentrism.*

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«No puedo enseñar nada a nadie, solo puedo hacerles pensar.»

Sócrates

«Solo podemos conocer de los objetos lo que hemos depositado en ellos.»

«Vemos las cosas, no como son, sino como somos nosotros.»

Immanuel Kant

Introducción

Relacionar educación y conocimiento podría parecer una obviedad; no obstante, dada su polisemia, un tratamiento riguroso de ambos vocablos requiere, por razones de espacio, acotar y precisar significados como condición de factibilidad de este trabajo. Para tal efecto se parte del aforismo sobre el ideal de la educación que ha inspirado a pensadores y que, al menos en lo discursivo, aún goza de aceptación. Lo fraseamos así: *«forjadora de las fuerzas liberadoras hacia el progreso de la condición humana».* Este aforismo realza el papel formativo y movilizador de la educación en la búsqueda del progreso que implica, necesariamente, el desarrollo del pensamiento crítico como base de un conocimiento liberador. El problema para avanzar en esa dirección surge cuando concienciamos que la idea de progreso predominante de nuestro tiempo reduce la superación de la condición humana a su connotación material y deja de lado el vacío existencial de sociedades deshumanizadas, privadas de auténticos valores de convivencia, con enormes y crecientes desigualdades, perpetradoras de la devastación planetaria en curso.

En este trabajo, el progreso de la condición humana se concibe como «florecimiento de los valores implicados en la superación espiritual, intelectual, moral y convivencial de las colectividades en armonía con el ecosistema planetario»[1], y lo designamos *progreso dignificante*; tal progreso, considerado como la razón última de la educación, será el trasfondo del desarrollo de este ensayo. Para entrar en materia, estas interrogantes alusivas al aforismo: ¿la educación que prevalece a escala global lo encarna?, ¿cómo entender la condición humana?, ¿qué es el pensamiento crítico?, ¿qué caracteriza a la educación que lo desarrolla?, ¿qué implica ese desarrollo para los distintos niveles educativos?, ¿qué caracteriza al conocimiento liberador? Las respuestas a estas preguntas serán el hilo conductor de este trabajo.

Características de la educación en nuestro tiempo

Captar la educación de las sociedades actuales para valorar su congruencia como «forjadoras de las fuerzas liberadoras hacia el progreso…» en su connotación espiritual, intelectual, moral y de convivencia comunitaria, requiere disponer de indicios reveladores de sus entrañas que no pueden provenir de lo que cada espacio o modalidad educativa afirma y difunde de sí misma, porque, si algo caracteriza a los planes de estudio, en particular de nivel superior y posgrado, es la incongruencia entre el «perfil del egresado» cargado de atributos casi sobrehumanos y su desempeño efectivo en lo profesional y social. En otros términos, la gran mayoría de los sistemas educativos en su aparente diversidad que se autocalifican «progresistas o innovadores» son equiparables por el tipo de desempeño ulterior del egresado, donde los perfiles están ausentes en medio de la degradación que prevalece[2]. De ahí la necesidad de escudriñar en las entrañas de lo social con arreglo a esta fórmula: *los rasgos distintivos de una sociedad en cierto periodo histórico son el indicio más revelador del tipo de educación que prevalece;* o en sentido inverso: *la educación realmente existente es espejo de la sociedad que la contiene*.

En la «civilización occidental» que se arroga la universalidad destacan tres rasgos como los más generalizados del momento histórico: 1) el «valor supremo» es el lucro y la ganancia a toda costa, y lo que no contribuya a los buenos negocios languidece o es inviable; 2) la dignidad humana es una mercancía en devaluación progresiva, prescindible y hasta desechable, y 3) la codicia insaciable que lucra con las peores causas, como son el hambre, la miseria, la infamia, las catástrofes, el tráfico de personas, el encierro carcelario, el tráfico de especies en riesgo o peligro de extinción, las guerras interminables, el terror generalizado o la devastación de los ecosistemas. Estos rasgos predominantes* son compatibles con este diagnóstico ineludible y revelador[3]: *«el mundo humano*

* Las excepciones más significativas y esperanzadoras son los pueblos originarios en todas las latitudes, porque encarnan una suerte de reserva moral de nuestra autodestructiva especie, priorizan en sus actividades el respeto y la preservación de la madre Tierra y, cada vez más conscientes de sus derechos, fortalecen su organización, actualizan sus usos y costumbres, se movilizan en defensa de sus territorios ancestrales y resisten la devastación, perfilando la simiente de un mejor mundo.

inmerso en una degradación omnímoda es evidencia del agotamiento y la ruina civilizatoria de la cultura dominante que, bajo el dominio implacable de los intereses de lucro sin límites, *ha convertido en mercancía lo más sublime y vil de la condición humana, y en rentables las peores atrocidades y la devastación planetaria*». Es ruina y no crisis de coyuntura porque el (des)orden imperante se muestra incompatible con la preservación de la vida planetaria, la humana incluida, y ha hecho añicos los valores dignificantes de la condición humana.

Si ahora reflexionamos sobre la *coincidencia* histórica entre la degradación extrema de la condición humana (con infinidad de matices), punto de llegada de un envilecimiento paulatino y progresivo, y las mayores cotas de educación superior y posgrado de las sociedades actuales como efecto de procesos formativos a lo largo de muchas generaciones, se nos revela una asociación inequívoca y directa de dos procesos coexistentes a escala global: el degradante y el educativo, lo que responde a la primera interrogante de la introducción: la educación se ha desentendido o ha fracasado en la formación de las fuerzas liberadoras hacia el progreso humano en lo espiritual, moral y convivencial, porque la presencia de tantos millones de egresados de la educación superior y de posgrado, lejos de hacerse notar como contrapesos efectivos a la degradación, ha sido mayormente silenciosa, lo que devela actitudes de negación, indiferencia, permisividad o complicidad[¶] con las fuerzas degradantes que subyacen al colapso civilizatorio. Esta conclusión argumentativa ineludible sobre el papel real —no idealizado— de la educación no deja de ser desalentadora para quienes nos empeñamos en superarla.

Ahora, si *los rasgos distintivos de una sociedad en cierto periodo histórico son el indicio más revelador del tipo de educación que prevalece,* es obligado percatarse de que el papel histórico de la escuela ha sido reproducir la cultura dominante del momento con su desigualdad social, sus usos y costumbres, y los saberes predominantes en los diversos campos[4]; o sea, la educación actual se muestra ajena y sin rumbo respecto al progreso humano porque, desde sus albores, la institución escolar ha sido configurada insensiblemente por la dominación —a espaldas de los deseos y las aspiraciones de sus integrantes— para perpetuar los intereses dominantes de turno[5]. Esta aseveración no pretende desalentar esfuerzos de superación de la educación en el plano social, sino alertar sobre la magnitud de los obstáculos y la necesidad de vincular esfuerzos que cristalicen en movilizaciones esclarecidas y coordinadas capaces de reencauzar el movimiento social.

Cabe preguntarse: ¿cómo se expresa la degradación en la escuela si, en términos generales, el profesorado respeta al alumnado y se afana en su enseñanza? La respuesta es que, lejos de implicar un envilecimiento directo y deliberado, favorece la reproducción de los *rasgos degradantes* que son basamento y anclaje de la degradación omnímoda y representan el *ethos* de la civilización actual[6]:

1) *Individualismo,* favorecido por una educación centrada en el individuo que solo por excepción promueve tareas y proyectos colectivos que fomenten la fraternidad y la cooperación. Se expresa en actitudes de «cada quien lo suyo y sálvese quien pueda», distantes de las reivindicaciones colectivas, de la solidaridad y la empatía, ajenos a acontecimientos que ocurren más allá del círculo cercano.
2) *Etnocentrismo* exacerbado con sus variantes culturales, sociales, confesionales, clasistas o raciales, raíz de las guerras perpetuas, el colonialismo, los fanatismos, el segregacionismo, el racismo, la discriminación, la xenofobia o el abuso.
3) *Especialización reduccionista y excluyente,* versión universal de la formación profesional como respuesta a los requerimientos de la división del trabajo y las exigencias del mercado, donde el especialista con visión parcial, sesgada, fragmentaria e inconexa no capta la raíz de los acontecimientos que lo sacuden y afectan; genera distancia o aversión al pensamiento complejo e integrador; desinteresado por entender su contexto histórico y social.
4) *Pasividad* ante los abusos del poder, cuya raíz es la limitación cognoscitiva del alumnado bajo una educación que prioriza el consumo y el recuerdo de información, ajena a sus intereses vitales y al pensamiento crítico. Así, el especialista juzga ajenos acontecimientos adversos y perturbadores, con actitudes de impotencia, conformismo, fatalismo y evasión.
5) *Competitividad* fomentada por la escuela y favorecida por el *individualismo,* que es espejo de un mercado de trabajo restrictivo e implacable que

[¶] Es obvio que, para la inmensa mayoría de los egresados de la escuela, víctimas de los mecanismos orwellianos de control de conciencias que se gesta desde la experiencia educativa formal, la degradación y el colapso son invisibles, su participación en las peores causas escapa a la conciencia y, por lo mismo, es mayormente indeliberada. También es preciso aclarar que la oposición a las fuerzas degradantes de grandes contingentes de la población no es resultado de su formación profesional, sino de búsquedas extraescolares y, con frecuencia, pese a la escuela.

fomenta la desunión, la rivalidad y la desconfianza (no la cooperación ni la solidaridad), que ha llegado a extremos de autocompetencia y autoexplotación (síndrome de *burnout*).

6) *Consumismo* inextinguible, real o imaginario, «carné de identidad universal», azuzado *ad nauseam* por los medios de persuasión, manipulación y desinformación que inducen necesidades ficticias y deseos imperiosos, e impulsan a satisfacerlos en un frenesí que desfoga angustias, mitiga ansiedades, propicia la evasión o frustra a los desheredados de la tierra. El consumismo es el sostén de una economía global que profundiza las desigualdades, agota los recursos naturales y devasta el planeta.
7) *Alta vulnerabilidad a la manipulación mediática* por multiplicidad de asuntos que escapan al entendimiento o carecen de interés cognitivo en un mundo polarizado que se percibe fragmentario e inconexo, enraizado en la *especialización reduccionista* y la *pasividad* que caracterizan a la educación predominante. Esta vulnerabilidad es aterradora en los tiempos que vivimos, cuando las guerras incesantes basan buena parte de su efectividad en la guerra mediática de desinformaciones y bulos que controlan conciencias de poblaciones inermes.

Los *rasgos degradantes* exhiben una marcada variabilidad entre países colonizadores y colonizados; en los primeros son más consistentes, acentuados y ampliamente generalizados (son originarios); en los segundos son inconsistentes, atenuados o ausentes en multitud de organizaciones y, particularmente, en un buen número de comunidades y pueblos originarios de la geografía planetaria que representan, en muchos casos, atisbos o proyectos hacia un mejor mundo.

La educación pasiva

¿Cómo designar la educación desentendida del ideal educativo de progreso humano que ha «coexistido pacíficamente» con la degradación hasta la debacle o, peor aún, que ha sido permisiva y hasta cómplice? La denominamos *educación pasiva* porque al tiempo que exige obediencia para cumplir su papel inculcador-reproductor de las ideas, prácticas y rasgos distintivos de la cultura dominante, ha inhibido en los educandos actitudes cuestionadoras de las imposiciones abusivas, arbitrarias e injustas o proactivas ante las dificultades u obstáculos, que ahora los convierte en dóciles consumidores de información heterónoma que integran legiones de especialistas competitivos, sumisos y explotables por un mercado de trabajo cada vez más restrictivo e inseguro. Así, la escuela, bajo la lógica del mercado, se convierte en fábrica eficiente de «mercancías competitivas» y reproduce la fuerza de trabajo actualizada y versátil que las empresas requieren, lo que explica la imposibilidad de la *educación pasiva* para contrarrestar la dominancia de los intereses de lucro sin límites y contribuir al auténtico progreso humano.

Para captar las razones que facilitaron y perpetuaron la sumisión de la escuela al poder y la dominación a lo largo de la historia, es preciso retrotraerse a los albores de la división del trabajo académico, cuando se *disociaron* producción (potestad de los espacios de investigación) y uso del conocimiento, donde la escuela asumió el encargo social de resguardarlo, acumularlo, ordenarlo y transmitirlo. Desde entonces, la escuela debió equiparar información y conocimiento, y favorecer actitudes dogmáticas con «las verdades establecidas». Prevaleció así la idea *pasiva* del conocimiento como adquisición y retención de información en detrimento de la *participativa:* elaboración propia de los educandos en forma de opiniones, ideas e iniciativas. Ahora, al especificar los caracteres de la *educación pasiva*[7] es preciso subrayar que, en situaciones concretas, no se manifiestan en estado puro ni en su totalidad, sino en forma de predominios y, dependiendo de la cultura y del nivel educativo, estos caracteres exhiben infinidad de variantes, matices e intensidades:

1) Un currículo fragmentado en multitud de temas y materias desvinculadas que, además, disocia teoría y práctica, dificulta en los educandos la comprensión del acontecer vital en el que están inmersos y genera desinterés y hasta recelo del pensamiento complejo, integrador y esclarecedor, lo que favorece una visión fragmentada e inconexa del mundo que pierde de vista la interdependencia de los acontecimientos, en especial aquellos que los sacuden y afectan, cuya resultante en los niveles superiores es la *especialización reduccionista y excluyente*.
2) Los temas de estudio (particularmente a nivel básico) suelen carecer de *sentido* para lo que más inquieta, conmueve, preocupa, despierta curiosidad, atrae o entusiasma a los educandos por su momento etario y circunstancias peculiares (experiencia vital), condicionando un aprendizaje superficial y fugaz que no deja huella, que «vacuna» contra el hábito de estudio o refuerza la idea de que en la educación no se aprende «lo importante para la vida» (raíz de la deserción escolar).

3) Desalienta o inhibe en los educandos el deseo de conocimiento que, en sus vivencias escolares, equivale a información carente de *sentido* para su experiencia vital que deben recordar cuando se les requiera (evaluación), ¡so pena de menosprecio o exclusión! De ahí su imposibilidad de distinguir los diversos tipos de conocimiento y reconocer el papel esclarecedor de las ideas y teorías comprensivas y explicativas en toda pretensión de conocimiento penetrante.
4) Para esta educación, conocer es adquirir y acumular información, y el recuerdo es la «potencia cognoscitiva» que se fomenta, lo que favorece la aceptación tácita y acrítica de las verdades establecidas, la inhibición de las potencias cognoscitivas basadas en la crítica y la gran *vulnerabilidad* de los educandos a la *manipulación mediática* que desinforma e induce creencias, prejuicios, filias, fobias o temores paralizantes.
5) Los docentes son los *protagonistas* del proceso y la enseñanza es la «fórmula idónea» de transmisión de los conocimientos que suelen carecer de *sentido* para la experiencia vital del alumnado porque suplantan sus inquietudes, incertidumbres o curiosidades suscitadas en el diario vivir, propias de su momento etario y de sus circunstancias peculiares de existencia («pedagogía de la suplantación»).
6) El papel del alumnado es, en principio, acatar las disposiciones formales: asiduidad, puntualidad, disciplina y dedicación; requisitos desproporcionados ante exigencias escolares de atender actividades impregnadas de aridez y rigidez porque se centran en transmitir una gran cantidad de información desprovista de *sentido* para su experiencia vital, que deben asimilar, acumular y, sobre todo, recordar cuando se les requiera (evaluación), y que lejos de suscitar motivación por el estudio y deseos de superación generan grados diversos de tedio, fastidio, desánimo o hasta rechazo.
7) El sistema escolar: organización, métodos pedagógicos, formas de trabajo, tareas o exigencias de rendimiento, al equiparar aprendizaje con recuerdo de información y, a mayor recuerdo, mayor éxito escolar, así se trate de recuerdos fugaces y evanescentes que no dejan huella, fomenta la *competitividad* por alcanzar distinciones, reconocimientos o evitar la exclusión, y el *consumismo* de información como recurso de «superación» que, aunado al que impera socialmente, apuntala el modelo económico del capitalismo salvaje que devasta el ecosistema planetario.
8) La evaluación, al operar como medio de control, clasificación, censura o exclusión de alumnos, lejos de encauzar el estudio compensatorio de los rezagos identificados o fomentar la crítica constructiva y la autocrítica (camino insustituible de superación), suscita sentimientos y actitudes negativas o de rechazo, que la desvirtúan en su papel clave de motivar y orientar el aprendizaje que se pretende.
9) La idea de progreso centrada en la disponibilidad de tecnologías de la información y la comunicación pierde de vista que «*la tecnología llega principalmente para suplantar, no para solventar nuestros problemas y aflicciones»,* y que «*el poder de las tecnologías solo se manifiesta bajo un uso selectivo, juicioso* y *cuidadoso*»[8]. Por ejemplo, de su uso en «tiempos pandémicos» no deriva equivalencia y menos ventaja sobre lo presencial; las interacciones directas mediadas por el respeto y la empatía son irreemplazables como fuentes de motivación, autoestima, confianza o estímulo para la superación. Este *tecnofetichismo* es contraproducente, desvirtúa la labor docente, potencia el *consumismo,* acentúa la dependencia tecnológica y favorece cuantiosas sangrías económicas en beneficio de las grandes plataformas digitales.
10) Los egresados de la *educación pasiva*‡ , aun de niveles superiores, por más que exhiban multitud de realizaciones y reconocimientos, difícilmente se sustraen a su «destino» de ser portadores de los *rasgos degradantes* y de proyectos vitales individualistas de «a cada quien lo suyo y sálvese quien pueda», «cómplices» de la dominación de los intereses de lucro sin límites que ha degradado todo a su paso.

A propósito de los egresados del nivel superior y de posgrado, los caracteres de la *pasividad* son extensivos, *mutatis mutandis,* a las diversas especialidades; por ejemplo, en *medicina,* la moda de las *competencias profesionales* no representa un cambio de fondo, sino que se trata más bien de adecuaciones del currículo a las necesidades del mercado que deja intocados los *rasgos degradantes* (¡en una profesión afincada en el humanismo!) y donde la *participación* basada en la *crítica,* aunque está presente en el discurso de los

‡ La idea de pasividad no se refiere a la mera receptividad o a la inacción de los alumnos; de hecho, pueden exhibir «febril actividad». El punto clave es que, en su papel asignado de consumidores acríticos de información, se les dificulta o aleja del desarrollo de las habilidades cognoscitivas basadas en la crítica, implicadas en la búsqueda y la elaboración de su propio conocimiento.

planes de estudios, tiene escasas posibilidades de ejercerse y desarrollarse. Cabe reconocer que muchos egresados se distancian de esos rasgos, pero por razones «extracurriculares» y bogando contracorriente.

El conocimiento en la superación de la condición humana

Ya se destacó la equiparación entre conocimiento e información según la *educación pasiva* imperante; ahora, al caracterizar una educación que sea «forjadora de las fuerzas liberadoras hacia el progreso de la condición humana», estas disquisiciones se refieren al conocimiento potencialmente liberador implicado en esta misión educativa, que es, justamente, el que aporta al esclarecimiento de tal condición más allá de los mitos prevalecientes. Así, dilucidar la condición humana —interminable por definición, dadas sus mutaciones históricas— implica, en principio, escudriñar *quiénes somos* (una reconstrucción a partir de lo que hemos sido como humanidad) y *dónde estamos* (un «diagnóstico» esclarecedor del estado actual del mundo y de nuestro planeta viviente), más allá de las ideas encubridoras y engañosas inculcadas por los medios masivos de persuasión y manipulación al servicio de la dominación.

Si bien ya se argumentaron el *agotamiento y la ruina civilizatoria de la cultura occidental* que da pistas de *quiénes somos* y *dónde estamos,* como se trata del conocimiento liberador y de la educación requerida, el *quid* es reconocer el punto de partida propicio, o sea, la *individualidad* en sus dos facetas, el *sí mismo* y su *contexto,* lo cual requiere precisiones: a) penetrar la individualidad es base del conocimiento liberador porque permite concienciar conflictos, inquietudes o aspiraciones; b) captar sus razones profundas obliga a incursionar en el mundo que habitamos[§] para esclarecer *quiénes somos* y *dónde estamos,* y c) el conocimiento del *sí mismo,* de *quiénes somos* y *dónde estamos,* es interdependiente, o sea, es ilusorio profundizar una complejidad en ausencia de la otra. La individualidad se esclarece penetrando ambas complejidades, descifrando lo que las configura de una manera y no de otra, que lleva, a la larga, a sumarse a las «fuerzas liberadoras» empeñadas en revertir la degradación, hacia un mundo igualitario y hospitalario.

Primar el conocimiento liberador en la escuela significaría un cambio radical de ese currículo escindido en disciplinas y materias inconexas que favorece una visión fragmentaria de los acontecimientos y oscurece su entendimiento, para dar lugar a otro que integre lo diverso y propicie que el alumnado desarrolle formas de *pensamiento complejo* como aproximación cognoscitiva, lo que implicaría un giro de los roles impuestos por la *educación pasiva:* el docente como «*protagonista* del acto educativo a través de la enseñanza y en tanto que depositario del saber», y el *discente* como «receptor *dócil* y consumidor *aquiescente* de información heterónoma». Tal cambio congruente con una educación liberadora significaría papeles bien distintos: el *educador,* lejos de centrarse en transmitir, informar, instruir, capacitar o suplantar a los alumnos, propicia, induce y encauza sus iniciativas de búsqueda y elaboración de su conocimiento, y el *educando* deja su actitud pasiva asumiendo, con creciente interés, *protagonismo* de su aventura cognitiva, lo que se sintetiza en esta sentencia: *la docencia realmente fecunda principia al incitar en los educandos la reflexión crítica y «contagiarles» entusiasmo por entender quiénes somos y dónde estamos*.

Al considerar que en los contenidos curriculares de la *educación pasiva* predominan los saberes científicos en especialización progresiva, podemos percatarnos de la distancia entre la educación imperante basada en un conocimiento atomizado, fragmentario e inconexo —incompatible con miradas abarcadoras y de conjunto—, y la «forjadora de las fuerzas liberadoras…» que implica propiciar en el alumnado el desarrollo de enfoques comprehensivos de los acontecimientos que lo acerque a esclarecer *quiénes somos y dónde estamos*. Dicho de otra manera, la pretensión de una educación liberadora es incompatible con los currículos actuales que priorizan los aportes de la ciencia moderna consistentes en miríadas de «hechos atomizados» de disciplinas desvinculadas, en detrimento de lo comprehensivo-explicativo donde radica el mayor potencial integrador de lo diverso y esclarecedor de lo complejo. Tal menoscabo en los currículos es revelador, por un lado, de la autoridad indiscutida de la ciencia *empirista* y *reduccionista* sobre otros saberes que, al arrogarse el monopolio del conocimiento verdadero

[§] Antropoceno es el nombre propuesto a inicios de este siglo para referirse a la edad geológica en que nos encontramos (la más reciente del Holoceno), alusiva a los cambios profundos y progresivos de los procesos regulatorios globales del planeta, provocados por la presencia humana, en particular a partir de la primera revolución industrial (1760-1840), que se expresan en el calentamiento global irreversible, la desertificación progresiva, el derretimiento de los glaciares, la polución sin freno del aire, las aguas y los suelos, la devastación de ecosistemas o la extinción acelerada de miles de especies.

y válido[9], ejerce poder de exclusión de lo que no se ciña a sus criterios de cientificidad; del otro, de la distancia que separa al conocimiento científico en su connotación actual de lo que proponemos como la finalidad suprema del conocimiento que aún concita aceptación, al menos en lo discursivo, en diversos círculos: *entendernos como humanidad fraterna y encontrar nuestro lugar en armonía con el concierto infinitamente diverso del mundo viviente,* donde las ideas integradoras basadas en la complejidad tendrían primacía.

Esta incompatibilidad del currículo con una educación liberadora se hace más ostensible al *coincidir* dos procesos inversos: a) el pleno desarrollo del *quehacer científico* que escudriña todos los espacios, inunda con sus miríadas de hechos revistas, libros y bases de datos, y sobre todo provee insumos para la innovación tecnológica donde las sociedades depositan lo esencial del progreso humano y su esperanza de un mundo mejor, y b) el devenir de la condición humana en inocultable decadencia, cuya degradación progresiva ha acompañado el colapso civilizador de la arrogante «cultura occidental» que ha degradado a un nivel sin precedentes la condición humana y ha perpetrado la devastación planetaria.

Tal *coincidencia* histórica muestra que, en la búsqueda del progreso *dignificante,* la *educación pasiva* imperante es un callejón sin salida: a) al asumir la superioridad cognitiva de la *ciencia moderna* propicia aprendizajes atomizados sin *sentido* para la experiencia vital de los educandos que, lejos de propiciar la reflexión intelectiva del mundo y de acompañar su búsqueda del bien vivir en aras de la superación de la condición humana, reproducen los *rasgos degradantes* que subyacen al colapso civilizador de la cultura imperante; y b) sus desarrollos curriculares, al primar las verdades establecidas depuradas de lo discrepante o «herético», y en especial de lo que «huela» a pensamiento complejo e integrador, dejan de lado lo controversial y cuestionador prescindiendo del principal incitador de la búsqueda de esclarecimiento del mundo que habitamos, que es condición del *progreso dignificante*.

Estos saberes que priman en la educación propician, en el alumnado, la *pasividad* ante el conocimiento porque entorpecen la reflexión y favorecen el consumo, la acumulación y el recuerdo (fugaz) de infinidad de datos de escasa relevancia para su *experiencia vital* —en menoscabo de ideas comprehensivo-explicativas y del pensamiento crítico— que lo hacen dependiente de información heterónoma.

El conocimiento potencialmente liberador

No basta que la docencia suscite en los educandos interés por entenderse y entender a través de ideas y teorías esclarecedoras —que no es poca cosa—; la clave está en incitarlos a ejercer el *pensamiento crítico* como hábito de estudio que, lejos de consumir, implica diferenciar, cuestionar y confrontar ideas en sus alcances y limitaciones. Esto supone ambientes propicios para la discusión y la deliberación colectiva entre pares. Aquí, el *desiderátum* es que los educandos desarrollen puntos de vista propios —puntos de llegada de sus reflexiones— que les den consistencia para *protagonizar* su aventura cognitiva. Este papel docente que motiva y encauza el *pensamiento crítico* y la elaboración del conocimiento de los educandos implica una concienzuda selección y secuenciación del material de estudio en la búsqueda de *sentido*** ; es decir, que los temas despierten vivo interés por su sintonía con lo que más les preocupa, inquieta, conmueve o entusiasma. El *sentido* hace que las tareas resulten interesantes, atractivas e incitantes para la reflexión introspectiva y la autognosis, vía de acceso al conocimiento de *quiénes* somos.

Dada su polisemia, precisamos nuestro concepto actual de *pensamiento crítico: forma de pensar metódica, cuestionadora, inquisitiva* y *propositiva* que convierte a quien la ejerce en *protagonista* de su propia aventura de esclarecimiento. Implica una *reformulación* del proceso de cognición en varios puntos:

1) Reconoce a la *afectividad* (favorable) como la fuerza motriz de todo esfuerzo cognoscitivo vigoroso y perseverante.
2) Destaca el papel clave de la *autocrítica* en el desarrollo del *pensamiento crítico.*
3) Prioriza el *pensamiento complejo (quiénes somos y dónde estamos)* como objeto de conocimiento.
4) Redefine los extremos del proceso (ignorados por otras corrientes), el «alfa»: *inclinación* a ponerlo «todo en cuestión» (convicciones, creencias, modas, ideas predominantes o formas de pensamiento único sobre diversas problemáticas que impone la cultura dominante), a *dudar* de lo «comprobado o definitivo» e *inquirir* la raíz de lo que parece «natural y evidente»; y el «omega»: *disposición anímica* a la ideación de alternativas que intentan superar

** El *sentido* potencial de un texto no radica, en principio, en datos numéricos, comparaciones o significaciones estadísticas, sino en ideas, sentencias o teorías que inciten la reflexión, a condición de que atañan a la *experiencia vital* de los estudiantes por su momento etario y circunstancias.

lo establecido (el potencial heurístico del *pensamiento crítico*). Entre «alfa» y «omega», el *pensamiento crítico* delibera, enjuicia, argumenta, debate, confronta o se posiciona por lo más revelador o esclarecedor.

5) Reconoce al *conocimiento liberador* como su *desiderátum* y auténtica *razón de ser.*

La divisa de la *educación pasiva,* «el conocimiento, al librarnos de la ignorancia, nos hace libres de elegir el propio camino de realización», al soslayar la crítica, lejos de liberar, convierte a los educandos en «terreno fértil» para la manipulación y el control de mentes y cuerpos que perpetúa la dominación de los intereses de lucro. Tal sujeción se gesta por la inculcación temprana de «dogmas y verdades» que afloran después como creencias y convicciones «propias». En palabras de Ortega y Gasset: *«Nuestras convicciones más arraigadas, más indubitables, son las más sospechosas*. *Ellas constituyen nuestro límite, nuestros confines, nuestra prisión»*[10].

La búsqueda de esclarecimiento: ¿Quiénes somos? ¿Dónde estamos?

Antes es preciso reconocer el principal obstáculo para encauzar a los educandos en el desarrollo del *pensamiento crítico* hacia un *conocimiento liberador:* el grandilocuente *proceso de enseñanza-aprendizaje,* pensado como *binomio* de términos unívocos y recíprocos, pues a mayor enseñanza, mayor aprendizaje, y viceversa, que representa el «dogma central» de la *educación pasiva* universalizada. Este dogma que subyace a la configuración de planes y programas de estudios a todos los niveles como esencia del acto educativo es *ilusorio* y *equívoco,* porque no existen tales univocidad y reciprocidad. Analicemos, a guisa de ejemplo, los modos habituales de alfabetizar: *enseñar a leer* a principiantes atosigándolos con lecturas de temas ajenos a su realidad deriva en un aprendizaje forzado, precario y efímero que no ancla en un deseo genuino por la lectura, percibida con indiferencia y desgano. También, *enseñar a escribir* con ejercicios tediosos y machacones de copiar «textos ilustres» resulta en aprendizaje maquinal, inconsistente, que no despierta interés por la escritura. Esta enseñanza que equipara aprendizaje con recuerdo y alumno con recipiente por llenar está presente, *mutatis mutandis,* en los diversos niveles educativos por más que se afirme que a nivel superior o de posgrado las cosas cambian radicalmente; si así fuera, no encontraríamos la «extraña» *coincidencia* de las más altas cotas históricas de educación superior y de posgrado a escala global con las más bajas respecto a la dignificación de la vida humana y planetaria.

Siguiendo con la alfabetización, otra historia sería si, en vez de «enseñar a leer» a las y los iletrados, se les despertara el interés por la lectura con textos atractivos, relevantes y «cargados de *sentido*» para su *experiencia vital* y sus circunstancias, que les motivaran a entenderse y entender a «otros», a captar las razones de sus conflictos internos y externos y cómo sobreponerse, a identificar los porqués de sus circunstancias de vida o idear opciones de acción y organización que mejoren su situación. En cuanto a la escritura, tampoco se trataría de «enseñarles», sino de animarles, persuadirles, apoyarles y encauzarles a expresar por escrito lo que les afecta, molesta, interesa, preocupa, desean o aspiran, para ir descubriendo las infinitas posibilidades de la escritura: compartir e intercambiar inquietudes, ideas, opiniones y puntos de vista, comunicar y compartir sentires, aclarar el pensamiento, encontrarse consigo mismos, ahondar el entendimiento de conflictos y problemas, o dar salida y elaborar emociones de todo tipo, en especial las perturbadoras. La *lectoescritura* así aprendida, que denominamos *lectoescritura inquisitiva* para diferenciarla de la idea predominante, es el medio por excelencia para ejercer el *pensamiento crítico* por la relación sinérgica entre sus términos: la *lectura,* fuente imprescindible de objetos cognitivos y blancos potenciales del *pensamiento crítico*; la *escritura,* forma de concretar, desarrollar, sistematizar y perfeccionar la *crítica* propositiva hacia formas superiores de pensar y de actuar.

En complemento, designamos *docencia incitadora* —contrastante con la *transmisora* propia de la *educación pasiva*— a esta forma de promover el aprendizaje de la *lectoescritura inquisitiva,* apelando al *sentido* de las tareas para la *experiencia vital* de los participantes e incitándolos a elaborar lo propio, la cual es privativa de la *educación participativa*[11] y coincidente con el aforismo socrático: *«no puedo enseñar nada a nadie, solo puedo hacerles pensar»*.

Si el «proceso de enseñanza-aprendizaje», lejos de ser la esencia del acto educativo, es un lastre hacia formas superiores de pensar y practicar la educación, cabe reconocer lo que hace a los textos, en potencia, *apropiados* y *pertinentes* para encauzar el protagonismo de los educandos en su aventura cognitiva vital. Como se trata de incitar y desarrollar el *pensamiento crítico,* un criterio de lo *apropiado* alude a ideas y teorías comprehensivas y explicativas cuya penetración estimule y desafíe las *operaciones intelectuales complejas,* cuya

cima es el *pensamiento crítico*; así, a mayor *complejidad* de las *operaciones intelectuales complejas* desafiadas por lo estudiado, mayor impulso hacia formas superiores de pensamiento. Ejemplos: a) textos que exigen comprensión y retención de significados explícitos —como los del nivel básico que apelan a la memorización— no desafían, mientras que los implícitos, que exigen interpretar y descifrar significados, son apropiados, como las máximas, los refranes o los aforismos desestimados por la escuela que, además de retar la interpretación, al adentrar en la sabiduría práctica y el sentido común aproximan al *quiénes somos;* b) los escritos descriptivos son insulsos, y en contraste, los conceptuales, que exigen enjuiciar, confrontar o posicionarse, son apropiados porque adentran en el pensamiento complejo. Lo *pertinente* de las lecturas es el *sentido,* condición necesaria para incitar el *pensamiento crítico* porque al tratarse de asuntos que les atañen, interpretan, deliberan y argumentan acuerdos o desacuerdos.

Sostener que las *operaciones intelectuales complejas* pueden incitarse, *mutatis mutandis,* desde temprano contradice lo establecido que las considera propias de la adultez, función de la educación superior (dicho sea de paso, tampoco se prioriza a este nivel el ejercicio sistemático del *pensamiento crítico*). Este dogma de la educación imperante que ha subestimado secularmente las posibilidades de la niñez que logra «lo imposible» respecto a las *operaciones intelectuales complejas*, en ambientes propicios —donde se les apoya y encauza— las tareas tienen *sentido* para su *experiencia vital*[12]; así, al ser interesantes constituyen desafíos *apropiados* y *pertinentes* que incitan el desarrollo incipiente del *pensamiento crítico*.

Problemática y temática prioritarias del conocimiento liberador

Primero una precisión, el vocablo *problemático/a* tiene dos acepciones principales: a) como sustantivo, conjunto de problemas por explicar, profundizar o resolver, propios de una disciplina, actividad u oficio; b) como adjetivo, carácter incierto, discutible, dudoso u objetable de ideas, opiniones, suposiciones o afirmaciones.

Ahora, respecto al *conocimiento liberador,* es preciso reconocer lo *problemático* de todo conocimiento con pretensiones de verdad —razón del extremo «alfa» del *pensamiento crítico*— al que aluden los dos epígrafes kantianos: *«solo podemos conocer de los objetos lo que hemos depositado en ellos»* y *«vemos las cosas, no como son, sino como somos nosotros»*. Ejemplos: a) el *racismo* que atribuye «inferioridad intrínseca» a grupos por su origen o apariencia es una «forma colonialista de ser»; b) el pensamiento que deposita «la idea de máquina» al entender a los seres vivos es, asimismo, el *ethos* científico de nuestro tiempo; c) el *antropocentrismo* que ve la naturaleza como «objeto de dominio a su servicio» la ha expoliado y convertido en vertedero de sus desechos. En cuanto a la relación con los demás seres vivos, el *antropocentrismo* está presente en la forma de pensarlos y valorarlos en función de su *utilidad* para satisfacer necesidades diversas: de un lado, domesticarlos y criarlos provocando plagas que diezman ecosistemas; del otro, subestimarlos, diezmarlos o extinguirlos.

La mirada antropocéntrica subyace a la relación perversa, predadora y abusiva de los humanos con el mundo natural que, aunada al capitalismo salvaje, ha provocado un calentamiento global irreversible y la devastación planetaria, indicios ciertos de la degradación humana hasta la ruina civilizatoria en que nos encontramos. Existen significativas excepciones: los pueblos originarios que se organizan y resisten el despojo y preservan tradiciones cuidadosas del ambiente, encarnan una especie de «reserva moral» de lo humano y germen esperanzador de un mejor mundo.

Con respecto al saber científico que se arroga la «exclusividad» del *conocimiento objetivo*[¶¶] en virtud de su labor experimental y detenta la máxima jerarquía entre los diversos conocimientos, lo que supondría que su problemática y su temática son simientes por excelencia del *conocimiento liberador,* tampoco escapa a ese carácter *problemático* porque ignora la influencia de convicciones, creencias, prejuicios o ideas en boga al decidir el problema a indagar, cómo abordarlo, la elección y el diseño del experimento, las tecnologías a utilizar, el análisis de los datos o la forma de interpretarlos; con dos agravantes: asegurar financiamiento y satisfacer criterios de publicación de revistas de alto impacto. Considerar que la objetividad sea inherente a la ciencia es ilusorio, y que la libertad de investigación es sino de nuestro tiempo, un mito encubridor. Otros rasgos *problemáticos* del saber científico que lo

[¶¶] La *objetividad* entendida como conocimiento del objeto en sí mismo, fuera del sujeto pensante o actuante, con independencia de sus dogmas, prejuicios, ideas interiorizadas, deseos, sentimientos o preferencias, es inasequible por definición; lo que sí está al alcance son aproximaciones efectivas a tal aspiración legítima que implican, en principio, ir develando la diversidad de influencias ignoradas que condicionan el acto de conocer, lo que se posibilita con el ejercicio del pensamiento crítico.

objetan como fuente del conocimiento liberador son: a) su fragmentación *ad infinitum,* que lo priva de *sentido* para la *experiencia vital* de los educandos, incapaz de retarlos a interpretar o externar opiniones, y b) su *empirismo reduccionista,* que desestima lo teórico explicativo, condiciona que su problemática y su temática operen como «auténticas vacunas» contra el pensamiento complejo e integrador.

La experiencia escolar

Incitar el *pensamiento crítico* en los educandos, desde el inicio, trastoca el «ritual *pasivo*» respecto al *proceso* y los *contenidos*:

1) El *proceso* de enseñanza-aprendizaje centrado en transmitir deja su lugar al que prima el desarrollo del *pensamiento crítico* que incita a dudar, cuestionar, no a consumir y acumular.
2) Los *contenidos*, ante el imperativo de desarrollar el *pensamiento crítico* y demás *operaciones intelectuales complejas,* son los que implican retos *apropiados* y *pertinentes* para tal efecto: a) lo *apropiado* alude al *pensamiento complejo* en los temas seleccionados por su mayor potencial esclarecedor del sí mismo y *su contexto* proyectado al *quiénes somos* y *dónde estamos*; b) lo *pertinente* radica en su *sentido* para la *experiencia vital* (*sintonía* con su momento etario y circunstancias), a fin de suscitarles un vivo interés por las tareas y dar viabilidad a sus opiniones y cuestionamientos por tratarse de asuntos que les atañen.

La alfabetización que incita a entenderse y manifestarse implica la *lectoescritura inquisitiva,* gran facilitadora del desarrollo del *pensamiento crítico* por las posibilidades de la *lectura:* fuente imprescindible de objetos de conocimiento y desafíos al *pensamiento crítico;* y de la *escritura:* medio insustituible para encauzar el *pensamiento crítico* que propone formas superiores de entender los objetos y actuar en consecuencia. Si los progresos de la *lectoescritura inquisitiva* son necesarios en el desarrollo del *pensamiento crítico,* se comprende la trascendencia de incitarla y desarrollarla, *mutatis mutandis,* a todas las edades a fin de erigirla como la herramienta cognoscitiva clave de la experiencia vital. Así, su progresión sería un recurso instrumental básico de la educación en los distintos niveles (cada nivel adelantaría en su dominio interminable), porque su despliegue en diversos ámbitos la configuraría como el *instrumento cognoscitivo* de mayor alcance y versatilidad para desarrollar el *pensamiento crítico* al superar desafíos crecientes: descriptivos, narrativos, analíticos, interpretativos, argumentativos, poéticos, conceptuales o teóricos explicativos, en sus afanes de penetrar o redefinir objetos de conocimiento. Incitar la *lectoescritura inquisitiva* al inicio es clave porque las *potencialidades cognoscitivas* aún no han sido inhibidas o suplantadas por imposiciones culturales.

Reconociendo sus antecedentes en el pensamiento de Paulo Freire[13,14], es momento de precisar las características del *conocimiento liberador:*

1) Su condición de posibilidad: el *desarrollo del pensamiento crítico* que penetra *quiénes somos* y *dónde* estamos devela lo que nos subordina o somete porque escapa a la conciencia y se experimenta como «lo real» o «lo propio», y nos alerta y pertrecha para concienciar la manipulación mediática y la desinformación que controlan mentes y cuerpos a escala planetaria.
2) Su fuerza creativa es la *acción transformadora:* la liberación no sería tal si se limitase a esclarecer los problemas que nos aquejan; supone acciones deliberadas, perseverantes y conjuntas hacia condiciones, circunstancias y situaciones progresivamente propicias para que tal proceso liberador interminable tenga lugar.
3) Su *carácter colectivo:* la facultad transformadora es propia de colectividades, confluencia sinérgica de individualidades transfiguradas por el *pensamiento crítico,* con proyectos vitales altruistas de alcance creciente en su poder transformador. (Una aclaración, la simiente del *conocimiento liberador* son las individualidades que desarrollan el *pensamiento crítico,* se adentran en el *pensamiento complejo,* esclarecen su situación en el mundo y la raíz de sus problemas, y emprenden acciones transformadoras conjuntas del *statu quo*.)
4) Su sustancia: el *pensamiento complejo* e *integrador,* en especial el que ha denunciado la *falacia antropocéntrica* y *etnocéntrica* como forma predominante de percibir el mundo y convivir en él (ver más adelante), que subyace a la destrucción de la naturaleza, a las guerras perpetuas (etnocentrismos) y a la degradación de la condición humana.
5) Su propósito *central:* dar forma a *proyectos vitales* colectivos empeñados en el *progreso dignificante* hacia la sublimación espiritual, intelectual, moral y convivencial de la condición humana, indisociable del cuidado y la preservación de la biodiversidad planetaria (lejos del que «deifica» la tecnología que contamina y devasta el planeta).

6) Su cualidad *valorativa*‡‡ : sin valores, toda realización del *conocimiento liberador* queda truncada, esclarecer los problemas no es fórmula infalible de las acciones transformadoras, los *valores* son imprescindibles para orientarlas. Por ejemplo, el *progreso dignificante* —cualquier opinión que merezca— implica asumir ciertos valores que subyacen a ese mundo utópico como horizonte de lo deseable que oriente a las colectividades en «su caminar inacabable» hacia tal *progreso,* señalice los avances y alerte de los retrocesos.
7) Su *razón de ser:* contrarrestar las fuerzas perpetradoras del colapso civilizatorio a fin de aproximarse al *progreso dignificante* para legar, a las futuras generaciones, un mundo donde florezcan comunidades dignificadas, esclarecidas, pluralistas, cohesivas, igualitarias, justas, cooperativas, fraternas y solidarias, cuyos integrantes compaginen lo laboral con la militancia en organizaciones gestoras de lo público y fiscalizadoras del poder, única garantía de vigencia y progresión de los derechos de la diversidad humana y de la preservación del ecosistema planetario.
8) Su *finalidad suprema:* «entendernos como humanidad fraterna y encontrar nuestro lugar en armonía con el concierto infinitamente diverso del mundo viviente».

Así entendido, el *conocimiento liberador* es, además de otra ontología humana, una utopía no por imposibilidad (numerosas ONG pugnan en distintos frentes por la dignificación de la vida, pero su dispersión y visión unilateral las enfrenta a «los síntomas y no a la enfermedad»: el capitalismo salvaje y el neocolonialismo, que limita sus alcances), sino porque especifica un ideal-horizonte capaz de motivar a inconformes con la educación imperante y orientarlos en un camino inédito hacia una educación liberadora a través del desarrollo del *pensamiento crítico,* que los incite a integrarse en colectividades diversas en la marcha interminable hacia el *progreso dignificante*.

Un paréntesis aclaratorio: ¿cómo armonizaría el *conocimiento liberador* con la formación de especialistas más y más diversificados que exige un mercado de trabajo cada vez más competido y constreñido? La eventual presencia social del *conocimiento liberador* solo puede ser resultado de procesos de transformación comunitaria —dilatados y accidentados— donde la formación especializada, moldeada por el *pensamiento crítico,* se haya dotado de una visión integradora y de una vocación cooperativa que confiera a los colectivos de especialistas un nivel superior de desempeño y trascendencia social vinculados por *proyectos vitales* conjuntos y altruistas en la búsqueda de un mundo dignificante para todas las formas de vida.

Primar el desarrollo del *pensamiento crítico* desde el inicio, al constituir una «herejía» al dogma de fe de la educación§§ , que reza «la esencia del acto educativo es el proceso de enseñanza-aprendizaje», amerita dos precisiones: a) la educación ha subestimado las potencias cognoscitivas de la niñez y reserva el *pensamiento crítico* a los adultos, y b) cuando el *sentido* está presente (sintonía con sus inquietudes e intereses del momento etario y las circunstancias), los educandos pueden ejercer una *lectoescritura inquisitiva* incipiente y externar opiniones y juicios sobre lo estudiado (preludios del *pensamiento crítico*). Desarrollar el *pensamiento crítico* en esta etapa implica disponer de desafíos pertinentes, como los derivados de encauzar la reflexión en dirección inversa a lo acostumbrado: de lo *individual* a lo *colectivo,* de la *interioridad* a la *exterioridad,* de lo particular a lo universal, de lo *micro* a lo *macro,* del *presente* al *pasado,* de una *complejidad menor* a otra *mayor,* o de la *experiencia* a la *teoría**** . A manera de cuestionamientos: *cómo* apreciar la historia sin escrutar el presente, *cómo* entender lo actual ignorando el pasado, *cómo* descifrar la historia sin los *etnocentrismos, cómo* penetrar lo social sin lo individual, *cómo* captar lo universal sin lo particular, *cómo* progresar en la *crítica* sin la *autocrítica, cómo* penetrar *quiénes somos* sin autognosis, o *cómo* pretender que

‡‡ Lo material es ajeno a este tipo de valores, es un presupuesto cuando se refiere a lo necesario para poder vivir con dignidad; en cambio, cuando constituye el centro de las aspiraciones humanas, como ocurre en nuestro tiempo, se convierte en un obstáculo mayúsculo al progreso como aquí se entiende.

§§ Este dogma también está presente, con muchos matices y de manera implícita o explícita, en los otros niveles, incluidos los planes y programas de estudios de nivel superior y de posgrado, y aun los elaborados según las principales corrientes pedagógicas contemporáneas, como el paradigma ecológico, las pedagogías críticas, el constructivismo o las competencias profesionales, porque lo importante no es lo que se dice, sino lo que se hace al interactuar con el alumnado.

*** Nótese que, en tales direcciones, los extremos de cada bipolaridad pueden tener efectos esclarecedores recíprocos y sinérgicos, que se anulan en el currículo pasivo porque invierte las direcciones o se desentiende de lo relativo a la autognosis y la autocrítica. Con respecto a la bipolaridad típica de la pasividad, de «lo simple a lo complejo» es aquí un despropósito porque la complejidad (un problema teórico) nunca es resultado de «conjuntar simplicidades empíricas».

el alumnado se interese por las ciencias cuando carecen de *sentido* para el momento etario de su *experiencia vital*.

Los componentes del currículo *participativo* son:

1) Su condición de factibilidad: a) un viraje de roles, el *docente* incita y encauza al alumnado a elaborar su conocimiento, y el *discente* protagoniza su aventura cognitiva; b) el *sentido* de los temas (sintonía con la experiencia vital del alumnado) es clave para «incitar, encauzar y protagonizar».
2) El desarrollo del *pensamiento crítico* y de la *lecto-escritura inquisitiva*, ejes del proceso educativo.
3) El *pensamiento complejo,* reto decisivo para ambos desarrollos.
4) El *conocimiento liberador:* desiderátum cuya realización extraescolar como *proyecto vital* conjunta lo laboral con lo social, que busca, en todos los frentes, contrarrestar las fuerzas degradantes y aproximarse al *progreso dignificante*.

Es momento de sintetizar las *revoluciones teóricas* que denunciaron la *falacia antropocéntrica* de superioridad de nuestra especie y la *etnocéntrica* de privilegiar unos grupos humanos sobre otros:

1) El heliocentrismo de Copérnico (siglo XVI)[15] trastocó el dogma monoteísta de que los humanos son cúspide de la creación divina y centro del cosmos.
2) *El origen de las especies,* de Charles Darwin (1859)[16], refutó el *creacionismo:* la especie humana no es designio del Creador, sino efecto de un proceso inmanente de la naturaleza preñado de contingencias (la evolución), o sea, el arribo humano no fue necesario, sino fortuito.
3) Para el *materialismo histórico* de Karl Marx (siglo xix)[17,18], el héroe, el gran hombre o el genio no son los protagonistas de la historia; es el *conflicto* entre etnias, castas o clases lo que la explica; el individuo no es el sujeto autónomo que decide su destino, es el ser social quien determina la conciencia y no a la inversa. A partir de Marx, el libre albedrío se convierte en ilusión y la conciencia en heterónoma.
4) Con Sigmund Freud (inicios del siglo XX) surge el *inconsciente*[19,20], espacio virtual donde se «esconden» traumas tempranos y otras piezas del rompecabezas afectivo del sujeto, que explica las motivaciones profundas del actuar humano; así, la conciencia no es solo heterónoma, sino también subsidiaria (del inconsciente).
5) James Lovelock trastoca (1979) la idea imperante de la vida en la Tierra[21]: la biosfera opera como «superorganismo» que ha regulado, por eones, el clima, la composición atmosférica y la química terrestre; la vida como fenómeno total creó las condiciones físico-químicas para su permanencia y evolución, y no a la inversa[22,23]; la Humanidad no es la especie superior, sino la *plaga primigenia,* que se reproduce sin control, contamina y devasta ecosistemas, perturba el concierto vital planetario y debilita el poder regulador de Gaia, del que depende la preservación de la vida, la humana incluida.

Tales revoluciones, que son aportes decisivos para «entendernos como Humanidad fraterna y encontrar nuestro lugar en armonía con el concierto infinitamente diverso del mundo viviente», huelga decirlo, no trascendieron al gran público ni sacudieron instituciones, ni dieron lugar a formas superiores de convivencia. Hoy día —salvo Gaia que se abre paso— son asuntos académicos, curiosidades históricas, o sea, el *antropocentrismo* y los *etnocentrismos* aún permanecen como *ethos* predominante de una Humanidad en guerras incesantes que todo lo degrada, como «prisiones de espíritus que aspiran a la liberación».

Epílogo

De inicio, unas interrogantes con propósitos esclarecedores:

1) ¿Cómo lograr que el currículo *participativo* influya progresivamente en la educación formal? El viraje ontológico del *docente* capaz de incitarlo en el *discente* supone procesos formativos respectivos divergentes de lo acostumbrado de largo aliento; es decir, no se trata de «todo o nada», su eventual presencia social implicaría cambios sociales profundos y progresivos que dieran surgimiento a asociaciones diversas empeñadas en el *progreso dignificante,* cuyo germen, en las aulas, serían *discentes* protagonistas de su aventura existencial esclarecedora, desarrollando su *pensamiento crítico* que, como colectivos maduros, habrían «revolucionado» a su paso el proceder de los distintos niveles educativos.
2) Si el desarrollo del *pensamiento crítico* es eje del currículo *participativo,* ¿cómo se articularían los niveles educativos en su perfeccionamiento y diversificación? Como progresividades sinérgicas a partir del nivel inicial; sin embargo, como los adelantos del nivel precedente condicionan los del subsiguiente, serían precarios en un solo nivel en ausencia de avances previos, y de ahí que penetrar el *sí mismo*, *quiénes somos* y *dónde estamos* como núcleo de

proyectos vitales que buscan el *progreso dignificante* deba incitarse temprano, cuando la autognosis y la autocrítica están facilitadas y las potencialidades cognoscitivas aún no han sido inhibidas o suplantadas por la enseñanza; así, el nivel inicial operaría como poderoso influjo transformador de los subsiguientes.

Un ejemplo de las limitaciones de desarrollar aisladamente el *pensamiento crítico* fue el *Seminario de Formación de Investigadores en Educación* (SEFIE) durante dos décadas[24], dirigido a docentes del área de la salud. El propósito del SEFIE era incitarlos a elaborar su conocimiento por medio del *pensamiento crítico* y la *lectoescritura inquisitiva.* Las tareas consistían en *criticar* investigaciones educativas, textos teóricos de educación, de metodología y epistemología, para elaborar puntos de vista propios y discutirlos con sus pares, en paralelo con el desarrollo de su proyecto de investigación. Como la mayoría carecía de experiencia en el *pensamiento crítico,* las expectativas sobre sus progresos eran cautelosas ante las obvias resistencias a la autocrítica, a aceptar la crítica o la inclinación inveterada a consumir y no a criticar; no obstante, con frecuencia nos sorprendían sus alcances y logros que proseguían con su propia labor docente. Ahora, una reflexión: ¿cómo sería el SEFIE en situaciones remotas de predominio social de la *participación*? Los alumnos, protagonistas de su aventura vital esclarecedora y habituados al *pensamiento crítico,* responderían a los retos del SEFIE con realizaciones dotadas de originalidad que representarían poderosos y renovados desafíos de superación del profesorado.

Un apunte más: ¿cuál sería el lugar de las ciencias en tales situaciones? Humanidades y ciencias sociales, por su *sentido* potencial, tendrían prioridad cronológica sobre las naturales; aunque lo decisivo sería la mutación operada en el espacio científico al ganar aceptación las teorías integradoras y transdisciplinarias†††[10], y el retiro del *empirismo reduccionista* como *ethos* científico, lo que implicaría formas bien distintas de entender la cientificidad, la naturaleza de los problemas de conocimiento relevantes o de interpretar el «significado» de los hechos científicos. Así, las ciencias no se estudiarían aisladas, sino como subconjuntos de una totalidad jerarquizada priorizando, en cada nivel, el de mayor *sentido* potencial para los *intereses cognitivos* de la *experiencia vital* del alumnado en cuestión.

Son tiempos de incertidumbre, de «guerras mediáticas» que controlan mentes imponiendo el pensamiento único sobre el acontecer mundial, donde «la verdad» es irrelevante; crecen la desigualdad, el despojo, la degradación y la devastación planetaria. La educación imperante se muestra indiferente o ajena al colapso civilizatorio; sus egresados, aun los profesionales con los más altos grados, exhiben un «analfabetismo crítico» que los convierte en víctimas de los dispositivos de control al servicio de la dominación; o sea, el derrotero que sigue la educación actual es inverso al de la *forja de las fuerzas liberadoras hacia el progreso de la condición humana,* se desentiende de la urgencia de preservar la vida planetaria y es ajeno al fin supremo del conocimiento: *entendernos como Humanidad fraterna y encontrar nuestro lugar en armonía con el concierto infinitamente diverso del mundo viviente*.

La educación *participativa* que promueve el protagonismo del alumnado en su aventura existencial de *esclarecimiento* por medio del *pensamiento crítico* —que ha mostrado viabilidad en ciertos espacios y momentos—, cuyo desiderátum es el *conocimiento liberador* hacia el progreso *dignificante,* constituye una propuesta utópica en el sentido de especificar un ideal-horizonte posible hacia donde caminar en la conformación de otra ontología humana que sustente ese progreso, y un clamor que busca despertar conciencias para emprender acciones al alcance con el fin de contrarrestar la debacle que nos arrastra y preservar la vida planetaria.

††† Perspectiva teórica con pretensiones esclarecedoras de cierta faceta del proceso vital, que integra y jerarquiza aspectos teóricos de diversas disciplinas, que disuelven su identidad, difuminan sus límites y derivan en síntesis penetrantes del objeto de conocimiento; así, por ejemplo, el *sí mismo, quiénes somos y dónde estamos* son construcciones transdisciplinarias. No confundir con lo *multidisciplinario*: conjunción de disciplinas, que preservan su identidad, para incrementar la comprensión del asunto en cuestión; ni con lo *interdisciplinario*, que implica puntos de contacto entre varias disciplinas, donde cada una aporta problemáticas o métodos para la resolución del problema identificado.

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RESEARCH ARTICLE

Patient-nurse ratio as an index related to healthcare-associated infections: a surveillance study

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Abstract

Background: *Healthcare-associated infections (HCAIs) are a hospital problem with a prevalence of approximately 5% in Mexico. HCAIs have been related to the patient-nurse ratio (PNR). This study aimed to analyze the association between PNR and HCAI in a tertiary-level pediatric hospital.* **Methods:** *We conducted a descriptive and prospective study at a tertiary-level pediatric hospital in Mexico. Nursing attendance and HCAIs records were documented from July 2017 to December 2018. PNR was calculated using nurse staffing records and patient census.* **Results:** *We obtained 63,114 staff attendance data from five hospital departments for the morning, evening, and night shifts. PNR > 2:1 was associated with a 54% (95% confidence interval (CI) 42-167%; p < 0.001) increased risk (odds ratio (OR)) for HCAIs, adjusted by shift staff, special conditions, and surveillance periods. The HCAIs more associated with PNR were urinary tract infections (OR 1.83; 95%CI 1.34-2.46), procedure-related pneumonia (OR 2.08; 95%CI 1.41-3.07), and varicella (OR 2.33; 95%CI 1.08-5.03).* **Conclusions:** *A high number of patients per nurse increased the probability of various types of HCAI. PNR needs to be established the HCAI guidelines and policies, as regulating the number of patients per nurse can prevent HCAIs and their complications.*

Keywords: *Cross infection. Patient-nurse ratio. Pediatrics. Nursing. Pediatric nursing.*

Proporción paciente-enfermera como índice relacionado con infecciones asociadas a la atención de la salud: un estudio de vigilancia

Resumen

Introducción: *Las infecciones asociadas a la atención a la salud (IAAS) son un problema para los hospitales; en México se ha reportado una prevalencia de alrededor del 5%. Las IAAS se han relacionado con el índice paciente-enfermera (IPE). El objetivo de este estudio fue analizar la asociación entre el IPE y las IAAS en un hospital pediátrico de tercer nivel.* **Métodos:** *Se realizó un estudio descriptivo y prospectivo en un hospital pediátrico de tercer nivel en México. Los registros de asistencia de enfermeras y de IAAS se documentaron desde julio de 2017 hasta diciembre de 2018. El IPE se calculó utilizando los registros de personal de enfermería y el censo de pacientes.* **Resultados:** *Se obtuvieron 63,114 datos de asistencia del personal de cinco departamentos del hospital para los turnos de mañana, tarde y noche. El IPE > 2:1 se asoció con un aumento del 54% (IC95% 42–167%; p < 0.001) de riesgo (razón de momios [RM]) para IAAS, ajustado por personal*

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de turno, condiciones especiales y periodos de vigilancia. Las IAAS mayormente asociadas con el IPE fueron infecciones del tracto urinario (RM 1.83; IC 95% 1.34-2.46), neumonía relacionada con procedimientos (RM 2.08; IC95% 1.41-3.07) y varicela (RM 2.33; IC95% 1.08-5.03). **Conclusiones:** *Un alto número de pacientes por enfermera aumenta las probabilidades de varios tipos de IAAS. Es fundamental que el IPE se establezca en las guías y políticas en materia de IAAS, ya que regular el número de pacientes por enfermera puede prevenir las IAAS, así como sus complicaciones.*

Palabras clave: *Infección cruzada. Índice paciente-enfermera. Pediatría. Enfermería. Enfermería pediátrica.*

Introduction

Healthcare-associated infections (HCAIs) are a severe problem worldwide. In the U.S., at least one HCAI is diagnosed every day in approximately one out of 31 hospitalized patients[1]. The mean prevalence of HCAIs is between 10 and 20%, according to different studies worldwide. Furthermore, the prevalence in intensive care units (ICUs) increases to 35-50%[2]. In Mexico, HCAIs prevalence is approximately 5%, although no specific ICU studies exist[3]. Among studies that included pediatric patients, the most frequent HCAIs were bloodstream infections, upper respiratory tract infections, and nosocomial pneumonia. The most frequent microorganisms responsible for these HCAIs were coagulase-negative staphylococci, enterococci species, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter* species[2].

Several studies have shown that HCAIs are preventable[4]. HCAI prevention strategies include hospital hygiene, hand hygiene, personal protective equipment, safe use and disposal of sharps, asepsis, assessment of the need for catheterization, catheter type selection, catheter insertion, catheter maintenance, and education of patients, family members, and healthcare personnel[5-7]. In addition, a poor patient-nurse ratio (PNR) has been associated with higher proportions of HCAIs[8-11].

More adequate human resources could be a strategy to prevent HCAIs. However, the need for more nursing personnel is global. The U.S. Bureau of Labor Statistics predicts that there will be a shortage of 11 million nurses[12]. The State of the World's Nursing reported a "shortfall of 5.9 million nurses" in 2020[13]; it is expected that "10.6 million nurses will be needed by 2030"[14]. According to the Organization for Economic Cooperation and Development (OECD), Mexico has 2.85 nurses per 10,000 inhabitants, a figure well below the global average of 9 nurses per 10,000 inhabitants[15]. High nurse shortage rates make it challenging to achieve the recommended PNR goals. For ICUs and emergency rooms, a ratio of one nurse for every 1-2 patients is recommended[16,17]. However, different reports show that this is not always achieved[18].

Few studies have demonstrated the correlation between PNR and HCAIs in the pediatric population. Some studies have addressed the relationship between nursing staff and specific HCAIs[19,20]. However, these studies were conducted in neonatal intensive care units (NICUs) or considered only one type of infection. More information is needed on poor PNR and its association with different HCAIs, specifically in the pediatric population.

Regarding the scarce evidence in the general pediatric population, we conducted a prospective analysis to address the association between PNR and HCAIs in a tertiary-level pediatric hospital.

Methods

We conducted a descriptive and prospective study in a tertiary-level pediatric hospital in Mexico. The emergency and surgery departments, surgical ICU (SICU), pediatric ICU (PICU), and NICU were included. Data were obtained from the nursing department attendance records and the epidemiology department surveillance records for 18 months.

The unit of study was the 24-hour day (considering morning, evening, and night shifts) in each hospital service (emergency, surgery, SICU, PICU, NICU). The primary outcome variable was the presence of one or more HCAIs per day and hospital unit.

We used the CDC/National Healthcare Safety Network (NHSN) definitions of HCAIs[21,22]. The HCAIs studied were catheter-associated urinary tract infections (CAUTI), urinary tract infections (UTI), hospital-acquired pneumonia (HAP), central line-associated bloodstream infections (CLABSI), varicella, occult bacteremia (OB), primary bloodstream infections (PBSI), and procedure-related pneumonia (PRP). OB was defined as the "presence of bacteria in the bloodstream of febrile children who have no apparent foci of infection"[23]. PBSI was defined as the "presence of viable bacterial or fungal microorganisms in the bloodstream (subsequently demonstrated by the positivity of one or more blood cultures) that elicit or have elicited an inflammatory response"[24]. PRP was considered in cases where pneumonia was documented 48

hours after specific procedures such as bronchial aspiration, foreign body extraction, intubation for surgical procedures, antisepsis practices at the time of intubation, and tooth brushing.

Previously, De la Rosa-Zamboni et al. described epidemiologic surveillance[7]. Trained nurses visited all wards three to four times weekly to detect suspected cases. Infectious disease physicians and specialized nurses from the Department of Health Epidemiology validated each suspected case of HCAI. The presence of infection was attributed to the three shifts from the three previous calendar days before the condition to determine the PNR for HCAI risk. For example, if the HCAI event was on day 25, the PNRs of the three shifts on day 22 were considered an exposure. Therefore, the unit of study was the workday that included all three shifts in each unit. The definition of HCAI and the day of the event were taken from the NHSH/CDC surveillance definitions at the time of the study[21].

The primary exposure variable was the PNR. The PNR was obtained by dividing the number of patients in a unit during a shift by the number of nurses in that same area and shift. The nurses who were not in charge of patients, i.e., those in charge of administrative tasks, were excluded from the analysis. The sources of information were the nursing department attendance records and the patient census. Nurse attendance was defined as the percentage of nurses arriving at work compared to those scheduled. In addition, if support nurses were sent to the units studied, these nurses were also considered in the calculation.

Other exposure variables considered for the study were absenteeism, number of patients on mechanical ventilation, number of nurses reassigned from their usual workplace to the units studied (nursing support staff), pre-scheduled nurse absences, seasonality, and the period when resident physicians begin their specialty. We considered seasonality a confounding variable due to the influence of weather on the rate of respiratory infections. November to January was considered the period of cold weather. In addition, during this period, there are more absences due to Christmas and New Year's holidays. June to August was considered the rainy season. We included nursing support staff since they are taken from units that may have different protocols and other types of patients, such as neonatal and surgical patients. From March to May, the period when residents begin their specialty was taken as an approximation of the adaptation time and learning curve of residents.

Statistical analyses were performed using Stata 15. We compared categorical variables with the χ^2 test and conducted univariate and bivariate analyses. We calculated odds ratios (OR) and 95% confidence intervals (CI) for the different HCAIs. We used logistic regression to estimate the OR and adjust for confounders. For specific analyses, the PNR was considered a quantitative variable, while for others, as a categorical variable categorized as follows: 1:1; 2:1; 3:1; 4:1, and ≥ 5:1. The variable HCAI was dichotomized into presence or absence. We performed a χ^2 test for the multivariate model to determine the association between variables and the outcome variable. If the association was significant, the variable was retained for model construction. These variables were added one by one to the model; if the risk (OR) changed substantially, i.e., more than 10%, the variable was retained. A likelihood ratio test was performed with each variable to determine if the models differed ($p < 0.05$).

Results

From July 1, 2017, to December 31, 2018 (549 days), 63,114 attendance entries were analyzed. The number of patient days during the study was 43,349, with a median of 17 hospitalized patients per day. Two hundred HCAIs were identified, 4.6 per 1000 patient days. The median of PNR was 2:1 (Table 1). This same table contains the data for each unit studied.

Differences were observed between the HCAIs rates of the units studied. The units with the highest rate of HCAIs were SICU and NICU. In contrast, the emergency unit showed the lowest rate of infections.

Absenteeism, a factor affecting the PNR, was 15.2% during the study period. This rate varied according to department and shift. The lowest absenteeism rate was recorded in the surgery unit during the evening shift, with only 6.3%, while the night shift from the same unit showed the highest rate of 30.7%. In all units studied, the night shift had more absences. For all shifts and units, the most frequent PNR was 2:1 (n = 3,388, 41.1%, $p < 0.001$). However, in more than half of the recorded nursing attendances (56.3%), more than three patients per nurse were registered, sometimes reaching seven patients per nurse (0.5%).

All studied units and shifts required at least one support nurse. The evening shift required the most nursing support staff: 48.6% (n = 1341, $p = 0.024$) of the required nurses covered by nursing support staff. The surgery department needed 69.1% (1,144) of nursing support staff. The SICU had the lowest staffing requirements;

Table 1. Baseline characteristics

	Total	Emergency	PICU	SICU	Surgery	NICU	*p*-value
Patient-days	43,349	9,678	4,704	4,074	12,476	12,417	
Hospitalized patients per day*	17 (9-23)	18 (14-22)	9 (8-10)	8 (6-9)	23 (21-25)	23 (20-25)	< 0.001
HCAIs, n	200	10	26	30	47	87	
Rate per 1000 patient-days	4.61	1.03	5.53	7.36	3.77	7.01	< 0.001
Assistance, n (%)							
Total	53,512 (84.8)	13,823 (85.5)	9,090 (82.4)	9,047 (81.3)	7,570 (84.7)	13,982 (88.3)	< 0.001
Morning	21,640 (90.2)	5,812 (90.9)	3,489 (87.0)	3,541 (88.7)	3,475 (90.7)	5,323 (92.3)	< 0.001
Evening	16,100 (90.3)	4,299 (91.0)	2,872 (89.6)	2,659 (84.4)	2,115 (93.7)	4,155 (92.4)	< 0.001
Night	15,772 (74.0)	3,712 (73.4)	2,729 (71)	2,847 (71.3)	1,980 (69.3)	4,504 (80.8)	< 0.001
Patients per nurse*							
Total	2.1(1.5-3.1)	2.3 (1.8-2.8)	1.4 (1.3-1.7)	1.4 (1.2-1.7)	4.2 (3.8-4.8)	2.6 (2.3-2.9)	< 0.001
Morning shift	1.9 (1.3-2.7)	1.9 (1.4-2.2)	1.3 (1.2-1.5)	1.3 (1.2-1.5)	4 (3.6-4.3)	2.4 (2.2-2.6)	< 0.001
Evening shift	2.3 (1.7-3.2)	2.5 (2-3)	1.6 (1.4-1.8)	1.6 (1.3-1.8)	4.4 (4.0-5.0)	2.7 (2.5-3.0)	< 0.001
Night shift	2.3 (1.5-3.3)	2.5 (2-3)	1.4 (1.3-1.7)	1.5 (1.3-1.8)	4.5 (4.0-5.0)	2.6 (2.3-3.0)	< 0.001

*Median (IQR).
**χ^2, Kruskal–Wallis. HCAI, healthcare-acquired infections; IQR, interquartile range; NICU, neonatal intensive care unit; PICU, pediatric intensive care unit; SICU, surgery intensive care unit.

the nurses in this unit covered 71% (1,177) of the staff requirement.

According to logistic regression, in the univariate analysis, PNR was positively associated with the occurrence of HCAIs (OR, 1.85; 95%CI, 1.59-2.15; $p < 0.001$).

In the multivariate analysis, the confounding variables fitting the model ($p < 0.05$) were the following: shift, patients with mechanical ventilation, nursing support staff, weather, previously planned absences, and the period in which the residents start their medical specialties. Adjusting for confounding variables in the model, the PNR was positively associated with the occurrence of HCAIs (OR 1.54; 95%CI 1.42–1.67; $p < 0.001$). Mechanical support increased the risk of HCAIs (OR 1.14; 95%CI 1.11–1.18; $p < 0.001$). Nursing support staff showed a borderline value ($p = 0.06$) for being a risk factor for HCAIs (OR 1.09, 95%CI 1–1.19) (Table 2).

The correlation between PNR and HCAIs showed a positive trend: the higher the number of patients per nurse, the higher the risk of HCAIs (Figure 1).

Univariate and bivariate analyses were conducted. These analyses showed that PNR is a risk factor for different HCAIs. A high number of patients per nurse increased the risk of CAUTI by 33% (95%CI 1.04-1.71; $p = 0.022$), of UTI by 82% (95%CI 1.34-2.46; $p < 0.001$), of HAP by 39% (95%CI 1.22-1.58; $p < 0.001$), of PRP by 108% (95%CI 1.41-3.07; $p < 0.001$), of varicella by 133% (95%CI 1.08-5.03; $p = 0.031$), and of CLABSI by 21% (95%CI 1.05-1.41; $p = 0.009$) (Table 3).

Table 2. Multivariate analysis of risk for HCAIs with PNR and with all the variables included in the model

	Variable	OR	*p*-value	95%CI
	PNR	1.54	< 0.001	1.42-1.67
Shift	Morning	1		
	Evening	0.66	< 0.001	0.53-0.81
	Night	0.63	< 0.001	0.51-0.78
Special conditions	Mechanical ventilation	1.14	< 0.001	1.11-1.18
	Nursing support staff	1.09	0.06	1.00-1.19
	Previously planned absences	0.91	0.41	0.72-1.14
Period	Cold weather season	1		
	Resident starting period	1.08	0.57	0.83-1.40
	Raining season	0.76	0.03	0.60-0.98

CI, confidence interval; HCAI, healthcare-associated infection; OR, odds ratio; PNR, patient-nurse ratio.
Logistic regression was performed with the variables that fit into the model.

Discussion

This study brought to light some interesting facts that had yet to be examined in the pediatric population in developing countries. We found that a higher number of patients per nurse on any given shift was associated

Table 3. Univariate and bivariate analysis of PNR with each type of HCAI, including nursing support staff

	Crude			Adjusted for supporting staff		
	Risk according to the PNR			Risk according to PNR including the nursing support staff		
	OR	CI	*p*-value	OR	CI	*p*-value
CAUTI	1.28	1.00-1.63	0.045	1.33	1.04-1.71	0.022
UTI	1.93	1.44-2.57	< 0.001	1.82	1.34-2.46	< 0.001
HAP	1.41	1.24-1.60	< 0.001	1.39	1.22-1.58	< 0.001
OB	1.05	0.92-1.20	0.446	1.05	0.91-1.20	0.48
PRP	2.09	1.43-3.05	< 0.001	2.08	1.41-3.07	< 0.001
Varicella	2.33	1.09-4.97	0.029	2.33	1.08-5.03	0.031
CLABSI	1.24	1.07-1.43	< 0.003	1.21	1.05-1.41	0.009
PBSI	1.50	1.31-1.72	0	1.44	1.25-1.66	0

CAUTI, catheter-associated urinary tract infection; CI, confidence interval; CLABSI, central line bloodstream infection; HAP, hospital-acquired pneumonia; OB, occult bacteremia; OR, odds ratio; PBSI, primary bloodstream infection; PNR, patient-nurse ratio; PRP, pneumonia related to procedure; UTI, urinary tract infection. These variables were explored using logistic regression.

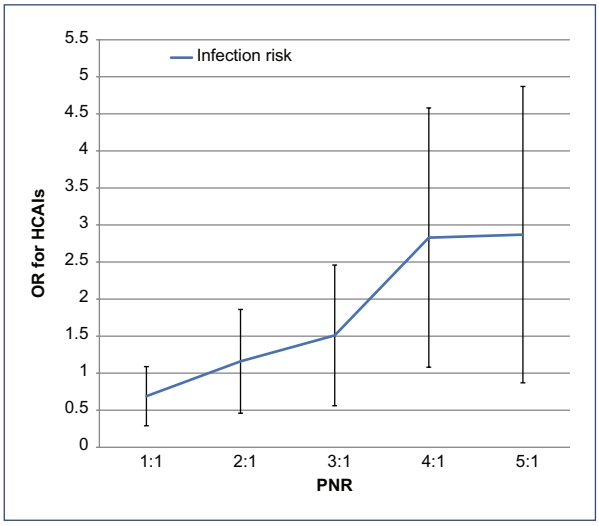

Figure 1. Risk of infection by PNR. Black lines indicate 95% confidence intervals (95%CI). HCAIs: healthcare-associated infections; OR: odds ratio; PNR: patient-nurse ratio.

with developing HCAIs. We also found that the risk of PRP and varicella infection doubled if the number of patients per nurse was high.

We found a positive association between a high number of patients per nurse and the risk of HCAIs; specifically, the risk increases when the PNR is ≥ 3:1. This aspect has hardly been described in the pediatric population. Tubbs-Cooley et al. (2019) found a mean PNR of 2:1 in a U.S. academic medical center and reported a negative correlation between this parameter and an acuity score ($p < 0.001$)[25]. However, this measurement was obtained only in the NICU, and they did not consider HCAIs as an outcome. In 2017, Tawfik et al. reported an association between HCAIs and California NICU nurses' perception of excessive workload. These authors stated that overwork might make nurses "less likely to notice errors or omissions in healthcare delivery," although they did not measure PNR[26]. Blot et al. found a relationship between PNR and ventilator-acquired pneumonia (VAP), but this study was conducted in an adult ICU. They reported fewer VAPs with a 1:1 PNR than when the PNR was >1:1 ($p = 0.002$)[27]. However, they did not address other types of HCAIs. Although we found that PNR increases the risk of PRP by 108% ($p < 0.001$), no association was found with different types of pneumonia. In 2011, Schwab et al. published a mean PNR in a study conducted in German ICUs similar to our research. They found that adequate PNR was associated with fewer cases of HCAIs; however, the association was lost in the multivariate analysis[28].

In this study, the increased risk of HCAI was maintained even in multivariate analysis, probably due to the presence of nursing support staff. We found that sending nursing support staff to areas with nursing staff shortages solved the problem. However, a marginally significant association between nursing support staff and HCAI risk was identified in the multivariate analysis

(OR 1.09, $p = 0.06$). Few studies have considered nursing support staff within their confounding variables. Bae et al. and Xue et al. did consider nursing support staff in their studies. However, they found no association between nursing support staff and HCAIs[29,30]. We propose that more extensive studies are needed to evaluate the role of support nurses and other factors, such as the preparation and expertise of supporting nurses to address this issue.

A higher risk of HCAIs was observed during the morning shift, independently of the other factors, and a lower rate of HCAIs in the emergency department. This finding could be associated with several factors not measured in the study because they are outside its scope. Such factors could be workload, sampling, medical rounds, and preparation of solutions and medications, among other procedures that may be more frequent in the morning shift. As for the emergency unit, they take fewer cultures. However, a limitation of our study is that these factors should have been measured. Further studies are required to analyze the risk of these factors.

When the types of infection were analyzed, hospital-acquired varicella and PRP were the HCAIs most strongly associated with PNR. Poor PNR doubles the risk of developing these infections. One hypothesis is that a higher workload is related to a lower adherence to protective equipment when caring for children with varicella and a lower adherence to hand hygiene. In the case of PRP, it could be that all necessary preparations for procedures, such as adequate oral care before surgery, were not correctly performed. Finding the causes of these infections should be the subject of future research, as these associations have yet to be described.

If a PNR of 2:1 is maintained most of the time, it will likely reduce the rate of HCAIs. The mean PNR in our study was 2:1, consistent with international guidelines and recommendations for ICUs[16,17]. However, in some shifts, there was a PNR of up to 7:1, which can be counterproductive for patients.

One of the limitations of our study was that there are other factors that, according to some authors, should be considered and should have been included. These factors include technological advances in healthcare, epidemiological profiles of the region, academic and professional staff profiles, and social, political, cultural, and health services[31-33]. As this is a tertiary-level hospital, the professional profiles are homogeneous within the services studied, and the included patients' and nurses' social and political context. In addition, the needs and complexity of each patient still needed to be addressed. However, all the services studied are critical care services, and a patient on mechanical ventilation was considered to need specialized and vital care. Finally, this study responds to what is experienced in many hospitals on a day-to-day basis since, in most hospitals, staffing is calculated by considering only the number of beds and patients with the traditional and pragmatic method[34]. The causes of absenteeism were not identified in this study, although it could be helpful to address this aspect in the future.

In conclusion, our data indicate that a high number of patients per nurse increases the risk of several types of HCAIs. Nurse staffing is critical for optimal patient care. Therefore, we strongly support the need to consider PNR in designing and implementing any HCAIs policy or preventive package.

Ethical disclosures

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

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

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

Conflicts of interest

The authors declare no conflicts of interest.

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RESEARCH ARTICLE

Effectiveness of printed infographics to promote breastfeeding in the Sonora population

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Abstract

Background: *In Mexico, the prevalence of exclusive breastfeeding for 6 months is low (28.6%); in the state of Sonora, it is only 15%. Effective strategies are needed to promote it. The aim of this study was to evaluate the effectiveness of printed infographics designed to promote breastfeeding in mothers from Sonora.* **Methods:** *We prospectively studied lactation regimes from birth. Intention to breastfeed, general characteristics of the mother-infant dyad, and telephone number were registered. Participants received educational training in the hospital; those assigned to the intervention group (IG) also received up to five infographic materials (designed and evaluated previously) in different perinatal periods, while those in the control group (CG) did not. At two months postpartum, the infant feeding practice and reasons for introducing formula were collected by phone. Data were analyzed with the χ^2 test.* **Results:** *Of 1705 women enrolled, 57% were missed during follow-up. Although 99% of participants planned to breastfeed, 92% of IG did so, compared to 78% of CG (95% Confidence interval [CI]: 7.04, 19.98; $p < 0.0001$). Mothers in the IG used more formula than those in the CG (6 vs. 21%; 95% CI: –20.54, –8.0; $p < 0.0001$), arguing insufficient milk production. The delivery of three infographics (one in prepartum and two in the hospital-training), or five infographics in different periods, promoted breastfeeding in 95% of participants.* **Conclusions:** *The distribution of printed infographics and initial training promoted breastfeeding, although not its exclusivity.*

Keywords: *Breastfeeding. Promotional infographics. Sonoran mothers.*

Efectividad de la infografía impresa para promover el amamantamiento en la población de Sonora

Resumen

Introducción: *En México es baja la prevalencia del amamantamiento exclusivo durante 6 meses (28.6%); en el estado de Sonora, solo es del 15%. Se requieren estrategias efectivas para su promoción. El objetivo de este estudio fue evaluar la efectividad de la infografía impresa diseñada para promover el amamantamiento en madres sonorenses.* **Método:** *Estudiamos prospectivamente la lactancia desde el nacimiento. Se registraron la intención de amamantar, las características generales de la díada madre-hijo y el número telefónico. Las participantes tuvieron capacitación educativa en el hospital; las asignadas al grupo intervenido (GI) recibieron además hasta cinco materiales infográficos (diseñados y evaluados en un estudio previo) en diferentes periodos perinatales, mientras que las del grupo control (GC) no los recibieron. A los dos meses posparto se consultó telefónicamente el tipo de alimentación infantil y los motivos para introducir la fórmula. Los datos se analizaron con la prueba de χ^2.* **Resultados:** *De las 1705 mujeres reclutadas, se perdieron el 57% en el seguimiento. Aunque el 99%*

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del total de las participantes planeó amamantar, el 92% del GI lo hacía a los dos meses posparto, en comparación con el 78% del GC (intervalo de confianza del 95% [IC95%]: 7.04 a 19.98; p < 0.0001). Las madres del GI usaron menos lactancia con fórmula que las del GC (6% vs. 21%; IC95%: –20.54 a –8.0; p < 0.0001), argumentando insuficiencia láctea. La entrega de tres infografías (una en preparto y dos en capacitación), al igual que cinco infografías en diferentes periodos, promovió el amamantamiento en el 95% de las participantes. **Conclusiones:** *La distribución de infografía impresa, además de la capacitación inicial, promovió el amamantamiento, aunque no su exclusividad.*

Palabras clave: *Amamantamiento. Infografía promocional. Madres sonorenses.*

Introduction

The postnatal period is a critical window in human development that impacts immediate and future health. According to the popular DOHaD theory, exclusive breastfeeding can modulate infant development. Breast milk components influence epigenetics, inducing the expression of genes associated with healthy development when the maternal diet is adequate[1].

A great problem in Mexico is that the rate and duration of exclusive breastfeeding up to 6 months is 28.6% (ENSANUT, 2018-19)[2], while Sonora, in Northwest Mexico, has one of the lowest rates, with just 15% of infants breastfed up to 5 months of age[3]. Thus, it becomes necessary to promote breastfeeding. The *Hospital Integral de la Mujer del Estado de Sonora* (HIMES), a major public hospital in Sonora, has implemented the Baby-Friendly Hospital Initiative. However, this initiative, by itself, does not guarantee continuity of breastfeeding for up to 6 months if extra support is not provided, such as an educational strategy from pregnancy through postpartum. Initially, the strategies would help the mother to change negative perceptions and increase her confidence to feed her child. Then, in the early postpartum, the strategies would help to solve immediate problems to continue breastfeeding[4].

Previously, we conducted a follow-up study with Sonoran mothers to register the reasons for discontinuing breastfeeding. To tackle them, we designed infographics and evaluated their acceptability qualitatively[5]. Thus, this study aims to analyze the effect of these materials on promoting breastfeeding at two-month postpartum as reinforcement of the health system's strategies.

Methods

Participants

Women who attended their pregnancy and childbirth at HIMES were recruited during the prenatal and postpartum visits and at the "*fiesta de egreso*" ("discharge party"), a service provided by health personnel for puerperal women before discharge, with training on health promotion topics, such as breastfeeding (Fig. 1).

Study design

We conducted a prospective study with non-randomized sampling. We worked with two groups of women: (a) intervention, which received a routine verbal educational hospital-training before discharge by health personnel, plus at least one of five infographics promoting breastfeeding delivered in different moments from pregnancy through postpartum by a lactation consultant with a brief counseling talk, and (b) control, which only received the routine educational hospital-training by health personnel. We assigned women who agreed to participate to the intervention group (IG), and once completed, we conformed to the control group (CG). The study participants were blinded to the intervention.

Printed infographics and time of delivery

For breastfeeding promotion, we used five printed materials pre-validated for this population: two short comics and three infographic cards illustrated in color[5]. While women were waiting in the pre or postpartum visit at the hospital, a person trained in breastfeeding counseling promoted its practice, using the corresponding infographics for that moment as support. Thus, general information was provided at the stage of pregnancy, trying to raise awareness about the importance of breastfeeding. Afterward, infographics were given with particular topics, as detailed.

From 28 weeks of gestation onward, women contacted at the prenatal visit received the "Breastfeeding is essential" card, which highlighted the benefit of breastfeeding, the average amount of milk produced for Sonoran mothers, and the infant's growth (Fig. 2). At the end of the hospital-training session, women were

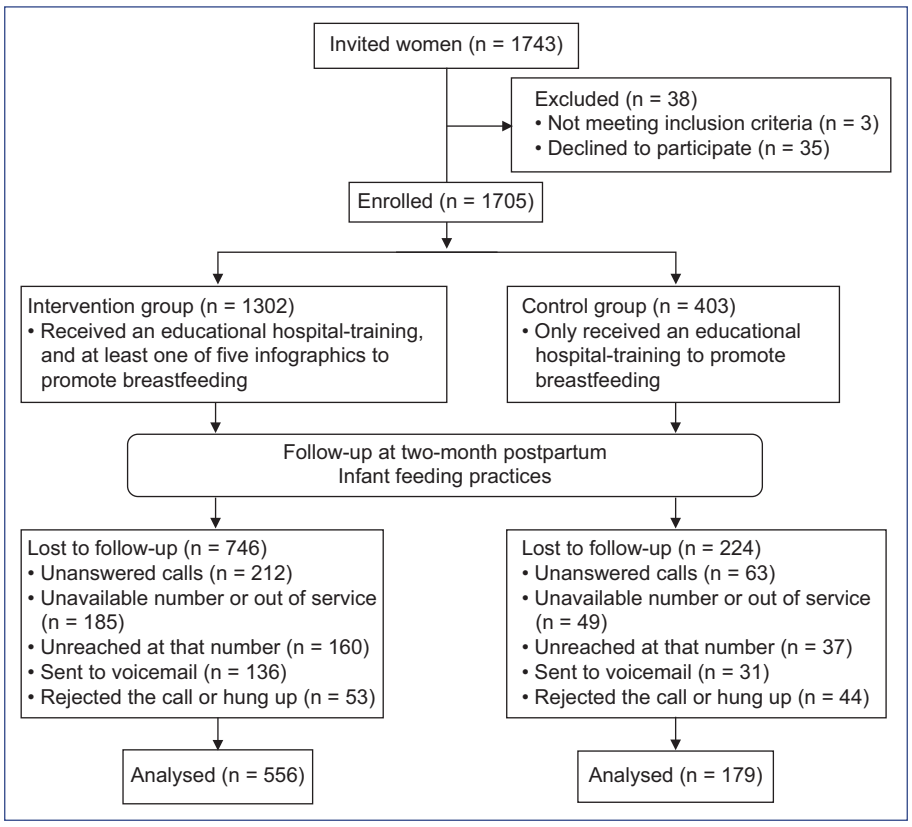

Figure 1. Participant flow chart.

asked to stay for a moment so we could reinforce the information on breastfeeding with the card "How to take care of your breasts" and the short comic "Won't Carlitos fill up with my milk?", which showed the correct latching on to the breast and encouraged confidence in the mother to satisfy her child (Figs. 3 and 4). During the postpartum visit, which took place from 7 to 15 days after delivery, the card "Your milk is enough!" provided the signs of good breastfeeding and recommendations for increasing milk production, and the short comic "Breast care for breastfeeding" told a story about how to tend sore and cracked nipples[5].

Data registration and consent

After signing the informed consent, the mothers' names, ages, dates of delivery, and intention to breastfeed were registered. Participants were informed that they could withdraw from the study at any time. We requested a telephone number for follow-up two months after delivery. When calling, women were asked what foods they were feeding their child, and then the type of feeding was classified. Those participants not contacted after three attempts to call were excluded from the study. The call attempts were made on different days of the week, at two-month postpartum.

Infant feeding practices

Exclusive breastfeeding was considered when the infant consumed only breast milk. Predominant breastfeeding when in addition to breast milk, small amounts of water, tea, and fruit juices was given. Mixed breastfeeding when breast milk was fed along with infant formula. Infant formula feeding when formula was the only food. Complementary feeding when the infant consumed milk and any solid or semi-solid food[6].

Data analysis

Continuous and categorical variables were described as mean ± standard deviation (SD) and percentages. The Chi-square test was used to compare infant feeding practices at two-month postpartum between the study groups. The significance level was set at $p < 0.05$. The NCSS v.2007 statistical package was used.

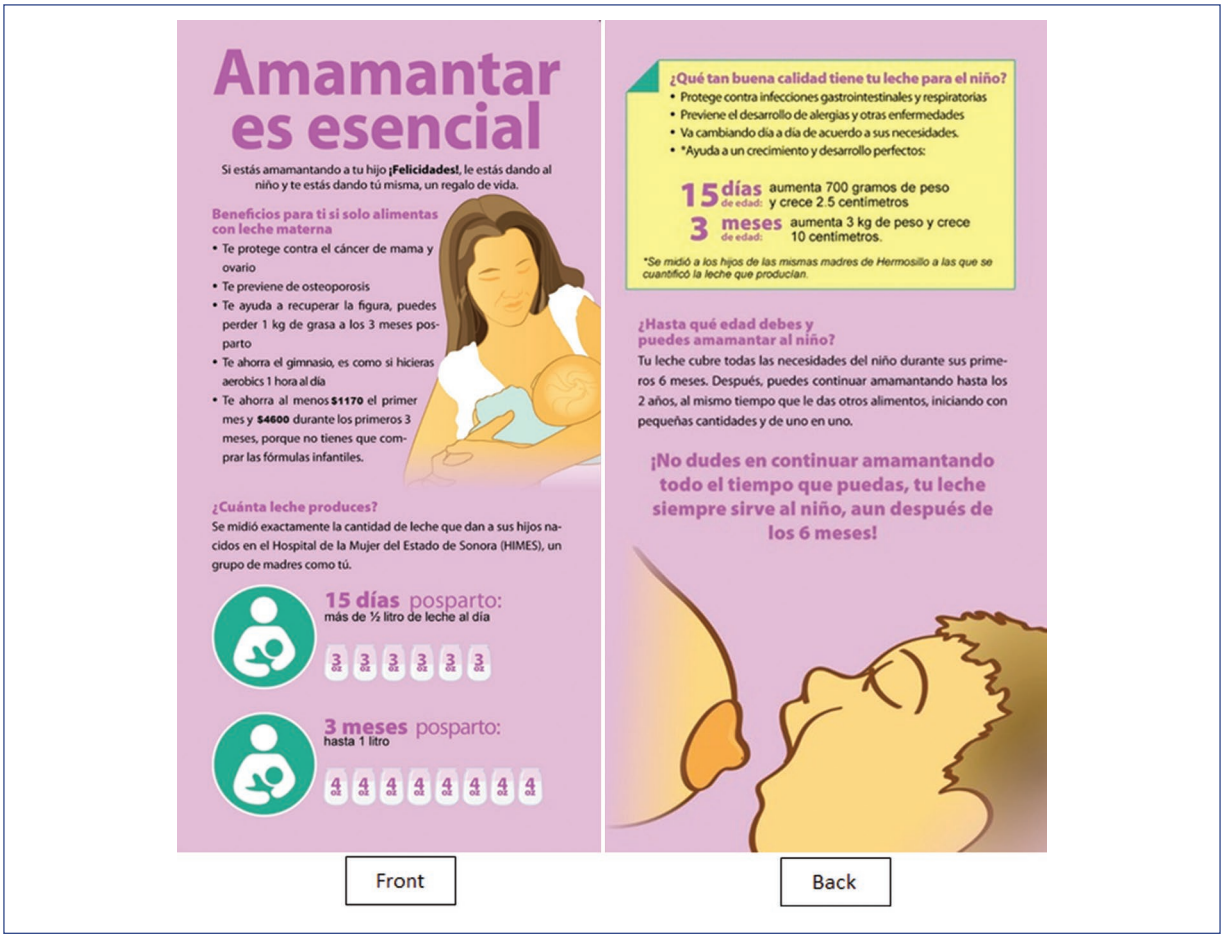

Figure 2. Infographics delivered at prenatal visit.

Results

Population studied

A total of 1705 women were enrolled, of which 99% intended to breastfeed. The IG included 1302 women recruited at the prenatal visit (n = 432), hospital-training (n = 743), and postpartum visit (n = 127). The CG included 403 women enrolled in the hospital-training.

At follow-up, more than half of the participants in both groups were lost: 746 (57%) of the IG and 224 (56%) of the CG. The main reasons were unanswered calls (28%), unavailable or out-of-service numbers (24%), and unreached women at the number provided (20%). We observed differences in the proportion of primiparous and multiparous and gender of newborns in the participant and non-participant women (Table 1). Participants were more primiparous women with female newborns, while those lost to follow-up were mainly multiparous with male newborns.

General characteristics of mother-infant dyads

We collected data on maternal and infant characteristics from 64% of the 735 mothers on follow-up (Table 2). The general characteristics showed homogeneity between groups ($p > 0.05$). The mean age was 22.83 ± 5.81 years, 55% were non-primiparous, and 38% were delivered by cesarean section. The groups were comparable concerning the sex of the newborns.

Delivery of printed infographics

A total of 1,051 mothers received the infographics at least once, 209 mothers received them twice, and 42 received the five infographics.

While delivering the infographics during the postpartum visit, positive feedback was received on the materials provided before. Among others: "*I am going to try this way, only to breastfeed*," "*Yes, it was beneficial to know this, because now I know I can produce good milk*."

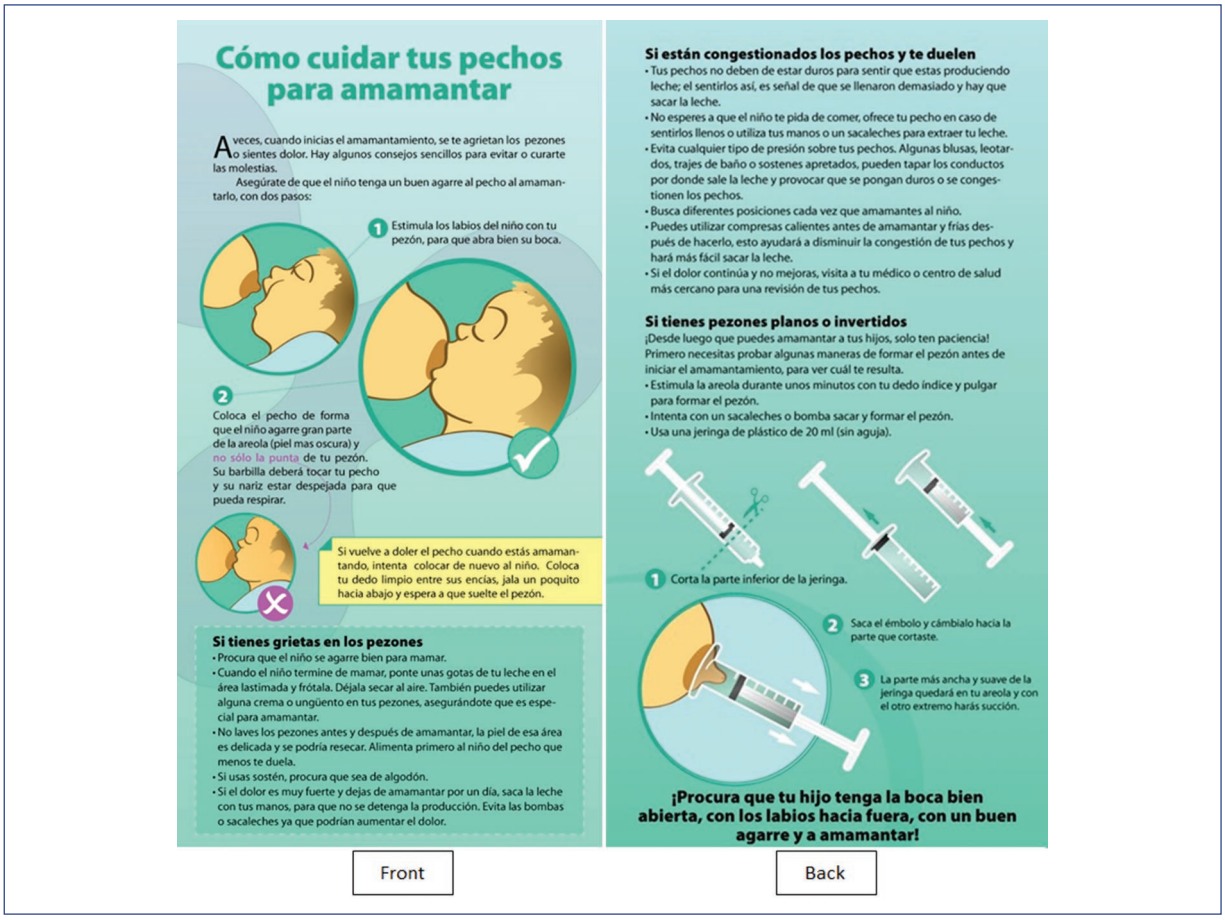

Figure 3. Infographics delivered at the end of the training at the hospital (discharge party).

Infant feeding practices at follow-up

Mothers with infographics breastfed more ($p < 0.0001$) than those of the CG (Table 3); with at least one of the printed infographics, 91.7% of the intervened mothers breastfed, compared to 78.2% of the CG. Unfortunately, the infographics did not influence the regimen being exclusive or predominant. In either group, it was equally mixed ($p > 0.05$), with more than 60% of infants supplemented with formula. However, the IG fed less formula ($p < 0.0001$).

Over 1% of the children received complementary foods as "little bites," regardless of the study group (Table 3). The rationale for early food introduction ranged from giving fruit porridge "*to keep the child happy*," or "*to get the child used to it*," to "*to see how the child responded*."

Infographics delivery effect on breastfeeding

Table 4 shows both the number of infographics and the time of delivery, according to the rate of breastfeeding (exclusive or predominant and mixed). The highest rate (95.6%) belonged to the mothers that received the five materials during the prenatal visit, the training session, and the postpartum visit; this was similar to the 95.3% of those who received three materials during the prenatal visit and the hospital-training session.

Reasons to introduce infant formula

In nearly 50% of the sample studied, the reasons for supplementing formula were insufficient milk production and a feeling that the infant was not satisfied (Table 5). The number of mothers arguing "*my milk was not coming in*" or "*the baby could not latch on*" was lower in the IG than in the CG. Sickness of the child or mother, "*my milk dried up*," returning to work or school, and medical advice were reasons given at a higher rate in the IG.

Discussion

Overall, the response from the women to participate in this study was positive. Recruitment was higher at

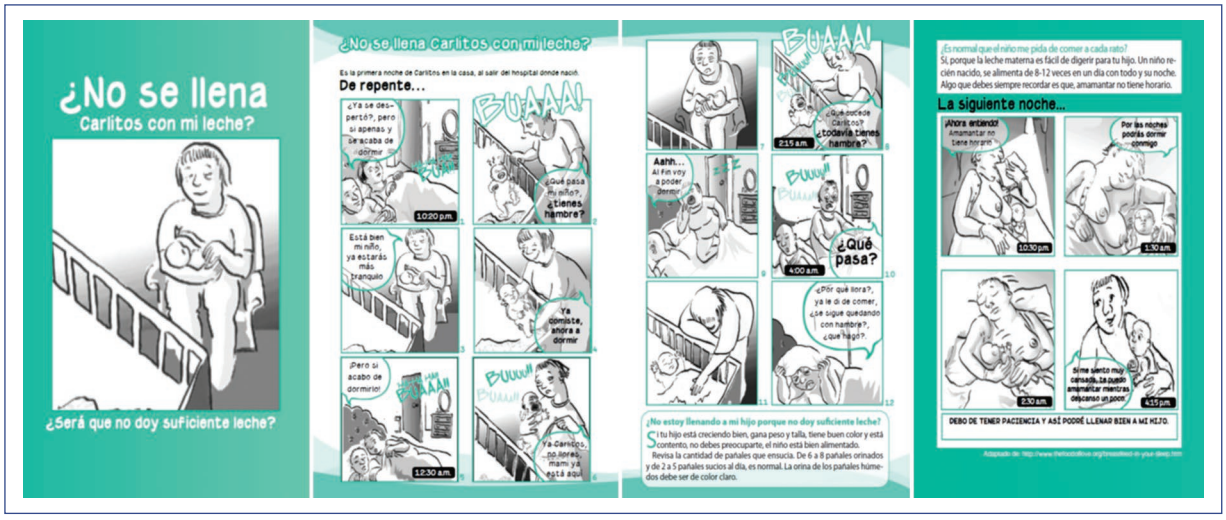

Figure 4. Comic delivered at the end of the training at the hospital (discharge party).

Table 1. Maternal and infant's characteristics by women who participated in the study and those lost during follow-up

	Participants (n = 472)	Lost during follow-up (n = 970)	Confidence interval 95%	*p*-value
Maternal age, years (mean ± SD)	22.77 ± 5.11	22.79 ± 5.84		
Infant sex, n (%)*				
Female	232 (49.15)	285 (29.38)	0.1443, 0.2511	0.0001
Male	245 (51.9)	699 (72.06)	–0.2548, –0.1484	0.0001
Parity, n (%)				
Primiparous	210 (44.49)	374 (38.55)	0.0051, 0.1137	0.0312
Multiparous	262 (55.50)	596 (61.44)	–0.1137, –0.0051	0.03112
Mode of delivery, n (%)				
Vaginal	291 (61.65)	587 (58.45)	–0.0217, 0.0857	0.2455
C-section	181 (38.34)	403 (41.54)	–0.0857, 0.0217	0.2455

*19 pairs of twins. SD, standard deviation.

the hospital-training when they were discharged than at the postpartum visit because women attended a health center instead.

Sample loss at follow-up was high (57%), probably because it is not so easily acceptable in our culture to answer phone calls from an unfamiliar numbers. Since this is a sample of young women, contact through social media could be a strategy[7]. Video calls could be another, such as those utilized by Kapinos et al.[8], who achieved 92% of participation of invited women.

With the lack of information on women lost during follow-up, there could be a differential participation bias since those who dropped out were mostly multiparous. Women who had practice breastfeeding before have significantly different breastfeeding experiences and knowledge than those in their 1st time. Therefore, primiparous women might be more anxious and insecure affecting breastfeeding success[9].

The hospital where we conducted this study is a public assistance institution. On average, the number of c-sections performed is lower than the national average (48.8%)[2] for women between 20 and 49 years of age but more than double the rate suggested by the WHO (5-15%). This is an adverse factor in initiating breastfeeding due to extended hospitalization, medication, pain, and problems accommodating the infant because of the surgical incision. All this stress affects lactogenesis[10], which induces formula feeding.

Prenatal education is an important factor in promoting breastfeeding. It prepares the expectant mother for a

Table 2. Maternal and infant's characteristics by group of study

	Intervention group (n = 298)	Control group (n = 174)	Confidence interval 95%	*p*-value
Maternal age, years (mean±SD)	22.88±4.24	22.66±5.98		
Infant sex, n (%)*				
Female	148 (49.66)	84 (48.28)	–0.0797, 0.1073	0.7710
Male	155 (52.01)	90 (51.72)	–0.0905, 0.0963	0.9516
Parity, n (%)				
Primiparous	127 (42.62)	83 (47.70)	–0.1439, 0.0423	0.2836
Multiparous	171 (57.38)	91 (52.30)	–0.0423, 0.1439	0.2836
Mode of delivery, n (%)				
Vaginal	177 (59.40)	114 (65.52)	–0.1512, 0.0288	0.1870
C-section	121 (40.60)	60 (34.48)	–0.0288, 0.1512	0.1870

*5 pairs of twins. SD, standard deviation.

Table 3. Feeding practices at two-month postpartum

Mode of feeding	Intervention group (n = 556)	Control group (n = 179)	Confidence interval 95%*	*p*-value*
Any breastfeeding, n (%)	510 (91.72)	140 (78.21)	7.04, 19.98	0.0001
Exclusive or predominant breastfeeding, n (%)	190 (37.25)	51 (36.42)	–7.28, 8.94	0.8577
Mixed breastfeeding, n (%)	320 (62.74)	89 (63.57)	–8.94, 7.28	0.8577
Infant formula feeding, n (%)	36 (6.4)	37 (20.67)	–20.54, –8.0	0.0001
Complementary feeding, n (%)	10 (1.79)	2 (1.11)	–1.21, 2.57	0.5316

*X^2 test.

Table 4. Breastfeeding practice according to the quantity of printed infographics given at the prenatal visit, the hospital-training session, and/or during the postpartum visit

Number of infographics*	Time of delivery (n)	Breastfeeding n (%)
1	Prepartum (106)	94 (88.7)
2	Hospital-training (252)	229 (90.9)
2	Postpartum (67)	60 (89.5)
3	Prepartum + Hospital-training (43)	41 (95.3)
3	Prepartum + Postpartum (12)	11 (91.7)
4	Hospital-training + Postpartum (53)	46 (86.8)
5	Prepartum + Hospital-training + Postpartum (23)	22 (95.6)

*Infographics delivered at prepartum: "Breastfeeding is essential" card; at Hospital-training: "How to take care of your breasts" card + the short comic "Won't Carlitos fill up with my milk?"; at postpartum, "Your milk is enough!" card + the short comic "Breast care for breastfeeding".

positive experience. Gao et al.[4] demonstrated that prenatal breastfeeding education sessions improved breastfeeding latch skills in 88.5% of women, and 76.9% avoided nipple pain and damage, one of the primary difficulties lactating women face. Huang et al.[11] showed that individual prenatal breastfeeding education and postnatal breastfeeding support for 4 months resulted in 94.6% of women practicing breastfeeding on demand and produced a low incidence of cracked nipples (21%). Furthermore, postpartum counseling is crucial to motivate women who feel insecure but want to breastfeed or for whom breastfeeding is difficult or has negative experiences[12]. In our study, the delivery of infographics was institutionalized. Nevertheless, it was not possible to provide the complete materials to all the women as planned. However, women who received at least one of the infographics breastfed more at 2-month postpartum than those of the CG.

The printed infographics promoted breastfeeding, although not its exclusivity, possibly because its importance

Table 5. Reasons why mothers introduced infant formula

	Intervention group (n = 356)	Control group (n = 126)
Perception of insufficient milk production, n (%)	64 (17.97)	27 (21.42)
Infant's or mother's illness, n (%)	37 (10.39)	10 (7.93)
Prescription drugs, n (%)	12 (3.37)	4 (3.17)
Painful breasts and/or discomfort, n (%)	8 (2.24)	3 (2.38)
Flat or inverted nipples, n (%)	7 (1.96)	2 (1.58)
Perception of child not satisfied n (%)	108 (30.33)	35 (27.77)
"My milk dried up", n (%)	25 (7.02)	7 (5.55)
Breast or breast milk rejection, n (%)	21 (5.89)	9 (7.14)
Maternal decision, n (%)	20 (5.61)	8 (6.34)
"The milk did not let-down", n (%)	11 (3.08)	11 (8.73)
The infant could not latch on to the breast, n (%)	11 (3.08)	9 (7.14)
"To get the child used to the formula", n (%)	5 (1.40)	-
Return to work or school, n (%)	41 (11.51)	7 (5.55)
Medical advice, n (%)	24 (6.74)	6 (4.76)
When leaving home, n (%)	11 (3.08)	-
For convenience, n (%)	4 (1.12)	6 (4.76)
Other, n (%)	8 (2.24)	3 (2.38)

is not explicit in the materials since it was designed to overcome barriers to breastfeeding[5].

About 37% of mothers provided with the infographics practiced exclusive or predominant breastfeeding, a higher rate than the 29% registered by Hurtado-Valenzuela et al.[3] at 3-month postpartum in the same population. However, it was lower than the national average of 40%[2]. This is likely attributable to the fact that in this population, the use of tap water or chamomile tea is common in the 1st days of the child's life. Although this practice is not considered important by mothers, it is negative for the duration of breastfeeding[13].

The mothers in the CG clearly relied on infant formula as the only type of feeding at 2-month postpartum, similar in proportion to a study with follow-up at 4-month postpartum[11]. This did not occur in the IG, which reflects that the infographics helped to reduce this feeding practice. Despite the cost and being a low-income population, mothers may consider infant formula safe and modern, a behavior influenced by excessive marketing promotion in the media[14].

Lack of information on complementary feeding was notorious, with a small rate of children under 2 months of age being fed solid or semi-solid foods despite international organizations recommending its introduction from the 6th month of life onward, while breastfeeding continues[6], in agreement with the *Norma Oficial Mexicana* 043 (Mexican Norm on Nutrition 043)[15]. The early introduction of solids has a negative effect on breastfeeding. Lessa et al.[16] estimated a higher risk for discontinuing breastfeeding before 6 months of age, when solids were introduced before 4 months of age, than from 5 months onward.

Regarding the effect of the infographics, providing one piece of material at the prenatal visit and two during the hospital-training session would be the extra support needed to initiate and maintain breastfeeding. In this case, the 95% rate of breastfed children was similar to that obtained when mothers received five materials. Nonetheless, we also recognized that the training of women by the health personnel before discharge from the hospital was important to promote breastfeeding. The positive effect of the infographics might be because the information that they contained was appropriate to the sociocultural context of the women in this population. Their design and evaluation were carried out on mothers who

attended the same hospital. In addition, when they were handed out, women received a brief counseling talk about the information they contained, according to their stage (pre or postpartum).

Breastfeeding is a practice that any woman can carry out, except in special circumstances, but beyond the physiological process, sociocultural factors are important[17]. In our study, although the infographics promoted breastfeeding, they did not influence the perception of insufficient milk production, which has been reported before in this population[3,5].

In this study, insufficient milk supply did not lead to the abandonment of breastfeeding, but rather its supplementation with formula, as happens in other populations[11].

In both groups of our study, the reasons for supplementing with formula included returning to work or medical advice. Those causes are unrelated to the mother-child bond, so they cannot be changed by supporting the mother. Therefore, actions aimed at promoting breastfeeding should consider all the factors involved in the woman's environment, including support from health personnel[13,17].

A strength of this study is the recruitment of women at different moments (prenatal visit, hospital-training session, and postpartum visit) to deliver printed infographics to promote breastfeeding and the feedback received when new infographics were provided. Nonetheless, although we recruited a relatively large sample of mother-infant dyads, the phone calls were not an effective strategy for follow-up. The lack of information on women lost during follow-up could have caused a differential participation bias. In addition, the printed infographics did not focus on exclusive breastfeeding. Even when in the follow-up, we did not ask women of the IG about the classification of infant feeding, but rather the food they gave their children, we cannot be sure that they answered correctly to please the researcher.

In conclusion, the delivery of the printed infographics designed for Sonoran mothers, in conjunction with the hospital-training, promoted breastfeeding. Over 95% of mothers breastfed at 2-month postpartum when provided three materials: one during the prepartum visit and two in the hospital-training session. In addition, exclusive or predominant breastfeeding was higher in the intervention than the rate reported in previous studies in this population and was close to the national average.

Thus, we infer that it was possible to promote breastfeeding in this population with printed infographics. However, we need to improve the intervention strategy to avoid losses. First, it is necessary to adapt the infographics focusing on exclusive breastfeeding. Then, to deliver the infographics combined with individualized counseling sessions. The first one can be face-to-face during the prenatal visit at the hospital in the third trimester of pregnancy. Then, a second face-to-face session at the end of the training session at the hospital before discharge. From this moment onward, we might offer ongoing support by video calls or social media within the first postpartum days (7-15 days). For women who returned to the postpartum visit at the hospital, the session could be face-to-face for counseling and delivery of infographics.

Ethical disclosures

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

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

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

Conflicts of interest

The authors declare no conflicts of interest.

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RESEARCH ARTICLE

Factors associated with blood product requirements during the transoperative period in pediatric patients

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Abstract

Background: *The efficiency of blood products (BP) requisition in elective non-cardiac surgeries is inherently complex. Moreover, it is aggravated in the pediatric population. This study aimed to identify the factors associated with using less than the requested BP during the transoperative period in pediatric patients undergoing elective non-cardiac surgery.* **Methods:** *We conducted a cross-sectional comparative study including 320 patients undergoing elective non-cardiac surgery for whom BPs were requested. Low requirements were considered when less than 50% of the requested amount or no BPs were used, and high requirements when more than the requested amount was used. The Mann-Whitney's U test was applied for comparative analysis, and multiple logistic regression was used to adjust for factors associated with lower requirements.* **Results.** *The median age of the patients was 3 years. From 320 patients, 68.1% (n = 218) received less than the requested amount of BP, while only 1.25% (n = 4) received more than the requested amount of BP. Factors associated with transfusion of less than the requested BPs were prolonged clotting time (odds ratio (OR) = 2.66) and anemia (OR = 0.43).* **Conclusions:** *Factors associated with lower than requested BP transfusion were prolonged clotting time and anemia.*

Keywords: *Blood transfusion. Pediatric. Elective surgical procedures.*

Factores asociados a los requerimientos de productos sanguíneos durante el transoperatorio en pacientes pediátricos

Resumen

Introducción: *La eficiencia de la solicitud de productos sanguíneos (PS) en las cirugías electivas no cardiacas es, de por sí, compleja. No obstante, se agrava para la población pediátrica. El objetivo de este estudio fue identificar los factores asociados con la utilización de una cantidad de PS menor a la solicitada durante el transoperatorio en pacientes pediátricos sometidos a cirugía electiva no cardiaca.* **Métodos:** *Se realizó un estudio transversal comparativo donde se incluyeron 320 pacientes sometidos a cirugía electiva no cardiaca para quienes se solicitaron PS. Los requerimientos de hemoderivados se consideraron como menores cuando no se utilizaron o se utilizó menos del 50% de lo solicitado y como mayores cuando se utilizó una cantidad mayor a la solicitada. Se aplicó la prueba U de Mann-Whitney para el análisis comparativo y regresión logística múltiple para ajustar los factores asociados a la presencia de menores requerimientos.* **Resultados:** *La mediana para la edad de los pacientes fue de 3 años. Se transfundió una cantidad de PS menor a la solicitada en el 68.1% (n = 218) de los pacientes, mientras que se transfundió una cantidad mayor a la solicitada solo en el 1.25% de los pacien-*

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tes (n = 4). Los factores asociados con la transfusión de una cantidad de PS menor a la solicitada fueron tiempos de coagulación alargados (TCA) (razón de momios (RM) = 2.66) y anemia (RM = 0.43). **Conclusiones:** *Los factores asociados a una transfusión de PS inferior a la solicitada fueron el tiempo de coagulación prolongado y la anemia.*

Palabras clave: *Transfusión sanguínea. Pediatría. Cirugía electiva.*

Introduction

The aim of blood product (BP) transfusion should be the treatment of specific processes when there is no alternative therapy or it is not possible to wait for the response of other treatments[1]. The indication for transfusion should be established according to primary objectives: maintenance or increase of oxygen transport to tissues, control of bleeding, and normalization of coagulation disorders[2].

Although blood transfusion provides undeniable clinical benefits, it is not a risk-free process. Also, it involves the consumption of a resource that is difficult to replace and, on many occasions, scarce. Published reports on blood products show that approximately 60% of all blood transfusions are administered in the operating room. For these reasons, it is essential to adjust transfusions to the real needs of each case[3,4].

The decision on the amount of BP requested before elective non-cardiac surgery can be complex. In general, the recommendation is to have a sufficient stock of BP in case of an unforeseen event during surgery. However, sometimes these units are not used. This has resulted in staff overload, waste of reagents, depletion of blood bank resources, and additional financial burdens for the patient and the institution. In the literature, up to 70% of surplus requests for blood products have been reported in different institutions[5,6].

Requesting BPs and their quantity is part of the preoperative evaluation. Therefore, on many occasions, this decision depends on the anesthesiologist's or inexperienced physicians' judgment. Therefore, using strategies in which physicians can make data-driven decisions to identify patients at high risk for transoperative bleeding has been justified[7,8].

Knowing the proportion of surgical procedures with lower or higher BP requirements in pediatric patients and identifying the factors associated with such conditions may help both to create a strategy to guide physicians and unify BP request criteria based on the patient's presurgical status and to improve the efficiency of BP requests, which would reduce risks and costs for patients and institutions.

This study aimed to identify factors associated with lower-than-requested BP requirements in pediatric patients undergoing elective non-cardiac surgery during the transoperative period.

Methods

We conducted a comparative cross-sectional study in a tertiary pediatric hospital from January to December 2020. We included pediatric patients (0-18 years) undergoing elective non-cardiac surgery and with a BP request. We excluded patients with incomplete medical records.

We obtained demographic and anthropometric data from the clinical records: body surface area, laboratory values before surgery, surgical risk classification according to the American Society of Anesthesiologists (ASA)[9], type of surgery (minor or major), surgical service, and the BPs requested before surgery. From the surgical record, we obtained information on whether the patient received a transfusion, the BP amount used, and the cause of the transfusion.

Patients were classified by age group: neonates (< 28 days old), infants (1 month to 2 years), preschoolers (2 to 6 years), schoolchildren (7 to 10 years), and adolescents (11 to 18 years).

The following definitions were considered: major surgery was defined as any procedure performed in the operating room involving incision, excision, manipulation, or suture of tissue, requiring regional or general anesthesia or deep sedation for pain control. Anemia was considered as the presence of hemoglobin less than two standard deviations for mean age according to sex, thrombocytopenia as a platelet value < 100,000/μL, and prolonged clotting time as values less than the 5th percentile according to age[10,11].

A lower requirement was considered when no BPs or less than 50% of the requested quantity was used. Conversely, a higher requirement was defined when more BPs were used during surgery because transfusion was necessary.

Statistical analysis

The median and interquartile range were calculated for quantitative variables and percentages and

frequencies for qualitative variables. The Mann-Whitney's U test was used to estimate differences between the quantitative variables and χ^2 to compare qualitative variables between the group of patients with BP requirements according to those requested and the group of patients with BP requirements lower than those solicited during the transoperative period. The Mantel-Haenszel test calculated the odds ratio (OR) and confidence interval (95% CI) for overestimating BP requirements. Multiple logistic regression analysis was performed to identify the factors associated with lower BP requirements during the transoperative period. A *p*-value < 0.05 was considered statistically significant. STATA v.16.0 was used for statistical analysis.

This protocol was approved by the hospital's Research and Ethics Committee. Parents signed the informed consent form. Patients > 8 years of age also signed informed consent following the recommendations of the Declaration of Helsinki.

Results

We identified a total of 1609 patients scheduled for elective non-cardiac surgery. Of these patients, blood components were requested in only 320. No patients were excluded.

In these 320 patients, the female sex predominated (60.3%), with a median age of 3 years. The frequency by age group was 32.5% for infants, followed by 29.4% for adolescents. Most patients (88.1%) were scheduled for major surgery, and the surgical service that performed the procedure was general surgery (30%), followed by neurosurgery (21.3%) and oncology (17.8%). According to the American Society of Anesthesiologists physical status classification, 81.6% (n = 261) of the patients were classified as ASA 3.

Preoperative studies showed anemia in 34.7%, thrombocytopenia in 14.1%, and prolonged clotting time in 84.7% of patients. Approximately half of the patients (44.7%, n = 143) required blood products during the transoperative period (Table 1).

Regarding BP transfusion during the transoperative period, the amount of BP requested differed from the amount transfused in 69.4% (n = 222) of the patients. In 68.1% (n = 218) of patients, the amount of BP transfused was less than requested, and only four (1.2%) patients required more BP than requested.

Of the four patients who required more BP, two were neonates (< 5 days), one was an infant (12 months), and the other was an adolescent (11 years). One of the neonates presented severe enterocolitis with thrombocytopenia and hemorrhage during surgery, despite a platelet concentrate transfusion. The other neonate had cholestatic syndrome and showed hemorrhage during transoperative cholangiography, despite standard coagulation times and platelet count. The infant presented with an anorectal malformation and underwent a posterior sagittal anorectoplasty.

Table 1. General characteristics and preoperative studies of the patients

Characteristics	Total (n = 320)
Sex	n (%)
Female	193 (60.3)
Male	127 (39.7)
Age (years)	
Median (interquartile range)	3 (0, 11)
Age group	
Neonate	43 (13.4)
Infant	104 (32.5)
Preschool	50 (15.6)
School-age	29 (9.1)
Adolescents	94 (29.4)
Somatometry	Median (interquartile range)
Weight (kg)	14.0 (3.9, 38.3)
Height (cm)	87.0 (52.0, 137.0)
Body surface area (m^2)	0.60 (0.12, 1.86)
Surgical service	n (%)
General surgery	96 (30.0)
Neurosurgery	68 (21.3)
Oncology	57 (17.8)
Neonatology	44 (13.7)
Other*	42 (13.1)
Thorax	13 (4.1)
Type of surgery	n (%)
Major surgery	282 (88.1)
American Society of Anesthesiologists classification	n (%)
1	2 (0.6)
2	45 (14.1)
3	261 (81.6)
4	12 (3.7)
Preoperative studies	Median (interquartile range)
Hemoglobin (g/dL)	12.0 (10.3, 13.5)
Hematocrit (%)	36.0 (31.5, 40.5)
Prothrombin time (s)	12.7 (11.8, 14.0)
Partial thromboplastin time (s)	26.9 (24.7, 31.0)
International normalized ratio (INR)	1.1 (1.0, 1.2)
Platelets (x1000/mm^3)	292.5 (136.0, 411.5)
Diagnosis	n (%)
Anemia	111 (34.7)
Thrombocytopenia	45 (14.1)
Prolonged clotting time	271 (84.7)

*Other: plastic surgery, maxillofacial surgery, ophthalmology, orthopedics, otorhinolaryngology, transplantation, or urology.

The adolescent had a history of abdominal trauma and was scheduled for ileostomy closure; both patients showed adhesions, which caused more bleeding than expected.

When comparing the group of patients with BP requirements matching those requested and the group of patients with lower BP requirements, it was detected that hemoglobin (12.3 g/dL vs. 11.1 g/dL; $p < 0.001$), hematocrit (37.0% vs. 33.1%; $p < 0.001$) and platelet levels (308,000 vs. 250,500; $p < 0.001$) were higher in patients requiring less BP than requested. When comparing alterations according to pre-surgical studies, patients with lower BP requirements presented a lower proportion of anemia (28% vs. 49%; $p < 0.001$), thrombocytopenia (10.6% vs. 21.4%; $p = 0.010$), and more prolonged clotting time (89.4% vs. 74.5%; $p = 0.001$) than patients with BP requirements matching those requested. No other differences were observed between the groups (Table 2).

A multivariate analysis was performed to identify factors associated with lower BP requirements than those requested during the transoperative period. We determined that prolonged clotting time (OR = 2.66) increased the probability of ordering more than required. At the same time, anemia (OR = 0.43) was a factor that decreased the probability of requesting less than solicited (Table 3).

Discussion

Among the main findings of this study, we identified that the amount of BP requested differed from that transfused in 69.4% (n = 222) of the patients; of these patients, only 1.2% required more BP than requested.

Appropriate ordering of BP for administration during surgery can be critical and life-saving[12]. In the adult population, physicians adopt guidelines for preoperative BP ordering based on blood loss prediction, laboratory studies, and preoperative clinical assessment (local maximum surgical blood order schedule)[13,14]. However, in pediatric patients, blood ordering lacks guiding principles because children have smaller blood volumes, and minimal blood loss requires transfusion of blood components to maintain adequate tissue oxygenation[6,15]. Thompson et al. confirmed a tendency to request more blood components in younger patients[16].

A challenge currently faced is that 30-70% of the BP requested for different surgical procedures is not transfused. On the one hand, requesting more BPs than required could limit its use for other patients and increase hospital costs[17,18]; on the other hand, being unprepared for inadvertent events during surgery can put the patient's life at risk. In this study, we identified that the amount of BP requested differed from that administered in 69.4% (n = 222) of the patients, consistent with the literature.

Age (infants less than one-month-old) and ASA 4 have been reported as factors associated with the difference between the amounts of BP requested and administered[12]. However, these factors were not observed in the present study, probably because other elements were analyzed, such as altered preoperative studies, with which pediatricians attempt to make more objective decisions on BP requests, thus reducing the risk of age less than one month as a factor. Gálvez et al. analyzed trauma and severe emergency patients[12]. In contrast, our research, conducted in a tertiary pediatric hospital, included primarily patients with complex diseases and multiple comorbidities (n = 273, 85.3%) with a high ASA score (ASA 3-4).

Another critical fact to highlight is the need to document more on the relationship between hemoglobin levels, coagulation time and platelet values, and the risk of transfusion in the transoperative period[4,7,12,14,16,19,20]. In our study, anemia was a condition for which the probability of transfusion of BP less than requested decreased. This observation could be related to the surgeon and anesthesiologist being more aware of hemorrhage and hemodynamic instability. Therefore, any condition out of the expected is enough to initiate an early transfusion[1,21]. Contrastingly, in patients with renal and hemato-oncological diseases, which are frequent in our hospital, physicians avoid BP transfusions despite identifying anemia in the pre-surgical studies because this could lead to future complications due to an increased risk of transfusion reactions and graft-versus-host disease[22,23]. In these patients, BP transfusion is only performed in the case of hemodynamic decompensation unresponsive to other measures[24].

Moreover, the probability of hemorrhage in subjects with altered coagulation times is more challenging to identify. Therefore, in most cases, physicians request BP and evaluate the transoperative conditions (bleeding and vital signs) to transfuse. Thus, each patient's preoperative request for BP in clinical practice should be individualized.

Based on our results, the alteration in coagulation times was identified as the factor that mainly impacted the difference between the BPs requested and those used. This finding indicates adequate preparation of the patient who did not require a BP transfusion despite presenting this preoperative alteration. However, further

Table 2. Comparison of general characteristics and preoperative studies between patients with requirements matching those requested and those with lower requirements than those requested

Characteristics	Requirements for BP during the trans-operative period (n = 316)		OR (95%CI) Overestimation of requirements	*p*-value
	Matching requirements (n = 98)	Overestimation of requirements (n = 218)		
Sex, n (%)				
Female	61 (62.2)	128 (58.7)	1.15 (0.69-1.95)	0.554
Male	37 (37.8)	90 (41.3)	-	
Age (years)				
Median (interquartile range)	2 (0, 11)	3 (0, 11)	0.91 (0.53-1.57)	0.751
Age group, n (%)				
Neonate	13 (13.3)	29 (13.3)	0.99 (0.45-2.09)	0.385
Infant	37 (37.8)	65 (29.8)	-	-
Preschool	10 (10.2)	40 (18.3)	-	-
School-age	9 (9.2)	20 (9.2)	-	-
Adolescents	29 (29.6)	64 (29.4)	-	-
Somatometry				
Weight (kg)**	11.9 (5.5, 32.0)	14.5 (3.9, 40.0)	-	0.312
Height (cm)**	79.0 (52.0, 134.0)	89.0 (52.0, 138.0)	-	0.413
Body surface area (m^2)**	0.53 (0.31, 1.10)	0.62 (0.23, 1.28)	-	0.363
Surgical service, n (%)				
General surgery	25 (25.5)	68 (31.2)	-	0.096
Neurosurgery	25 (25.5)	43 (19.7)	-	-
Oncology	22 (22.5)	35 (16.1)	-	-
Neonatology	14 (14.3)	29 (13.3)	-	-
Other*	12 (12.2)	30 (13.8)	-	-
Thorax	0 (0)	13 (6.0)	-	-
Type of surgery, n (%)				
Major surgery	85 (86.7)	193 (88.5)	1.18 (0.52-2.53)	0.650
ASA, n (%)				
1	0 (0.0)	2 (0.9)	1.17 (0.49-1.19)	0.538
2	12 (12.2)	31 (14.2)	-	-
3	81 (82.7)	179 (82.1)	-	-
4	5 (5.1)	6 (2.8)	-	-
Preoperative studies				
Hemoglobin (g/dL)**	11.1 (9.5, 13.0)	12.3 (10.9, 13.9)	-	< 0.001
Hematocrit (%)**	33.1 (29.0, 38.8)	37.0 (33.0, 41.0)	-	< 0.001
PT (s)**	12.8 (12.0, 14.2)	12.6 (11.8, 14.0)	-	0.296
PTT (s)**	26.9 (24.6, 31.2)	26.7 (24.7, 31.0)	-	0.050
INR **	1.1 (1.0, 1.2)	1.1 (1.0, 1.2)	-	0.292
Platelets (x1000/mm^3)**	250.5 (114.0, 348.0)	308.0 (166.0, 428.0)	-	< 0.001
Diagnosis				
Anemia, n (%)	48 (49.0)	61 (28.0)	0.40 (0.23-0.68)	< 0.001
Thrombocytopenia, n (%)	21 (21.4)	23 (10.6)	0.43 (0.21-0.87)	0.010
Prolonged clotting time, n (%)	73 (74.5)	195 (89.4)	2.90 (1.47-5.70)	0.001

*Other: plastic surgery, maxillofacial surgery, ophthalmology, orthopedics, otorhinolaryngology, transplant, or urology.
**Median (interquartile range). Mann-Whitney's U test was applied for quantitative and χ^2 for qualitative variables. Mantel-Haenszel test was used to calculate the odds ratio (OR) and confidence interval (95% CI).
ASA, American Society of Anesthesiologists physical status classification; CI, confidence interval; INR, international normalized ratio; OR, odds ratio; PT, prothrombin time; PTT, partial thromboplastin time.

studies focused on factors that can better predict BP requirements in pediatric patients with altered coagulation times before surgery to ensure the efficient use of BPs.

One of the limitations of the present study is that transoperative hemodynamic considerations, such as amine requirement, total bleeding, and hourly diuresis, were not considered. These elements would provide

Table 3. Multivariate analysis to identify factors associated with a lower transfusion than the requested blood products (n = 316)

Characteristics	Coefficient (95% CI)		OR (95% CI)		*p*-value
Neonates and infants	-0.06	-0.57, 0.45	0.93	0.56, 1.56	0.808
Major surgery	-0.07	-0.84, 0.70	0.93	0.42, 2.02	0.856
ASA classification	0.04	-0.57, 0.66	1.04	0.56, 1.14	0.719
Thrombocytopenia	-0.45	-1.16, 0.26	0.63	0.31, 1.30	0.215
Anemia	-0.83	-1.36, -0.29	0.43	0.25, 0.74	0.002
Prolonged clotting times	0.98	0.30, 2.44	2.66	1.35, 5.25	0.004

95% CI, 95% confidence interval; ASA, American Society of Anesthesiologists physical status classification; OR, odds ratio.
Intercept: 0.32.

valuable information on the reasons for transfusion in this group of patients. Moreover, since this was a cross-sectional study, it was impossible to define the causality and temporality of the identified factors. For this reason, it is essential to continue with studies to identify predictive factors.

In conclusion, pediatric patients with anemia used the requested BPs more frequently than patients without anemia. However, patients with prolonged clotting time used the requested BP less often than patients without this factor. Therefore, we recommend that the request for BPs should be individualized in patients with prolonged clotting time scheduled for surgery. This practice will help blood banks to be more efficient.

Ethical disclosures

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

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

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

Conflicts of interest

The authors declare no conflicts of interest.

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RESEARCH ARTICLE

Concordance between referral and final diagnoses of pediatric patients with vascular malformations

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Abstract

Background: *Vascular malformations (VaM) are a heterogeneous group of disorders resulting from the dysmorphogenesis of blood vessels. Although correct classification is relevant to providing adequate treatment according to evidence-based medicine, diagnostic terminology may be misused or need clarification.* **Methods:** *We conducted a retrospective study to measure agreement and concordance between referral and final confirmed diagnoses of 435 pediatric patients with VaM newly referred to the multidisciplinary Vascular Anomalies Clinic (VAC) using Fleiss kappa (κ) concordance analysis.* **Results:** *We found fair concordance between referral and confirmed diagnoses of VaM (κ 0.306, $p < 0.001$). Lymphatic malformations (LM) and VaM associated with other anomalies showed moderate diagnostic concordance (κ 0.593, $p < 0.001$ and κ 0.469, $p < 0.001$, respectively).* **Conclusions:** *Continuing medical education strategies are required to improve physician knowledge and diagnostic accuracy in patients with VaM.*

Keywords: *Vascular malformation. Diagnosis. Clinical decision-making. Diagnostic errors. Pediatrics.*

Concordancia entre el diagnostico de referencia y final de pacientes pediátricos con malformaciones vasculares

Resumen

Introducción: *Las malformaciones vasculares (MVa) son un grupo heterogéneo de trastornos resultantes de la dismorfogénesis de los vasos sanguíneos. A pesar de que la correcta clasificación es relevante para brindar un adecuado tratamiento de acuerdo con la medicina basada en la evidencia, la terminología diagnóstica podría resultar confusa o utilizarse de manera inapropiada.* **Métodos:** *En este estudio retrospectivo se midieron el acuerdo y la concordancia entre los diagnósticos de referencia (o derivación) y los diagnósticos finales confirmados de 435 pacientes pediátricos con MVa recién remitidos a la Clínica de anomalías vasculares (CAV) multidisciplinaria, mediante el análisis de concordancia kappa de Fleiss (κ).* **Resultados:** *Se encontró una buena concordancia entre los diagnósticos de referencia (o derivación) y los diagnósticos confirmados de MVa (κ 0.306, $p < 0.001$). Las malformaciones linfáticas (LM) y las MVa asociadas con otras anomalías presentaron concordancias diagnósticas moderadas (κ 0.593, $p < 0.001$ y κ 0.469, $p < 0.001$, respectivamente).* **Conclusiones:** *Se requiere de estrategias de educación médica continua para mejorar el conocimiento de los médicos y la precisión diagnóstica de los pacientes con MVa.*

Palabras clave: *Malformaciones vasculares. Diagnóstico. Toma de decisiones clínicas. Errores de diagnóstico. Pediatría.*

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Introduction

Vascular malformations (VaM) are a heterogeneous group of disorders with endothelial cell dysmorphogenesis, classified as (1) simple, (2) combined, (3) of major named vessels, and (4) associated with other anomalies[1]. Their correct classification is relevant to provide adequate treatment according to evidence-based medicine. The International Society for the Study of Vascular Anomalies (ISSVA) periodically updates this classification to standardize terminology, including new genetic and clinical findings. However, physicians who are not familiar with these patients may need more clarification with diagnostic terminology to prevent inadequate evaluation, management, and prognosis[1-3].

This study aimed to measure the concordance between referral diagnoses of new pediatric VaM patients sent to the Vascular Anomalies Clinic (VAC) and the final confirmed diagnoses.

Methods

We conducted a retrospective study of 435 patients referred between 2012 and 2022 to our institution's Vascular Anomalies Clinic (VAC). First, we reviewed the diagnoses provided at the time of referral and then those established by our team according to the ISSVA after evaluating clinical, imaging, and histological findings. We used descriptive statistics and Fleiss kappa (κ) concordance analysis with the following interpretation: ≤ 0 indicated no concordance; 0.01-0.20, none to mild; 0.21-0.40, fair; 0.41-0.60, moderate; 0.61-0.80 substantial; and 0.81-1.00, near perfect concordance.

Results

Fifty-one percent of patients were female, with a mean age at initial diagnosis of 50.31 months (standard deviation (SD) ± 51.86). Simple VaMs were observed in 300 patients: 162 with lymphatic malformations (LM), 82 with venous malformations (VM), 46 with arteriovenous malformations (AVM), and ten with capillary malformations (CM). Combined VaMs were observed in 109 patients: 107 with slow-flow (CM ± LM ± VM) and two with high-flow. VaMs associated with other anomalies were identified in 23 patients, and provisionally not classified conditions were observed in three patients.

Fifty-eight percent of patients were correctly diagnosed with VaM. The rest of the patients were misdiagnosed, as they had a different condition: vascular tumor (17.4%), neoplasm (11.7%), cyst/abscess/infection (5.4%), and others (9.4%). Patients were referred by pediatricians (146), surgeons (146), dermatologists (61), and primary care physicians (30). Dermatology (62.2%), neonatology (50%), oncology (50%), surgery (42.8%), and pediatrics (38.3%) most frequently diagnosed patients correctly.

When analyzed by specific VaM subtypes, we found 53% of LM, 30.4% of VaM associated with other anomalies, 23.9% of AVM, 20% of CM, and 10.9% of VM were correctly diagnosed. Overall, the diagnostic concordance between referral and final diagnoses was fair (κ 0.306, standard error (SE) 0.064, $p < 0.001$); for LM and VaM associated with other anomalies, it was moderate (κ 0.593 and κ 0.469, respectively) (Figure 1).

Discussion

Suboptimal diagnostic concordance of VaM impairs communication, treatment, and research in this field[3]; a low yield of correct referral diagnoses of VaM has been reported. Greene et al. found that 45.6% of 3,645 patients were labeled correctly at referral, particularly LM (69.3%) and AVM (59.4%)[4]. LMs are frequent VaM[5] and, together with AVM, have distinctive clinical features, which may explain why they can be more frequently correctly identified. Only LM and VaM associated with other anomalies had moderate diagnostic concordance in our study.

Low diagnostic consistency has been reported even at centers with VACs. For example, Pahls et al. reported a concordance of 9%, reflecting physicians' lack of familiarity or resistance to adopting ISSVA terminology rather than insufficient knowledge[6]. Additionally, the correct diagnosis of VaM may be more problematic than tumors because they are less common, and physicians should be familiar with the full spectrum[4]. Vascular anomalies are only sometimes taught to medical students. Moreover, residents and specialty practitioners who care for these patients receive limited exposure and training[7].

The main problem of misdiagnosis is the impact on patient care. For example, patients with VaM may be misdiagnosed as infantile hemangiomas and prescribed ineffective medical treatment (Figure 2A) or diagnosed with neoplastic diseases and consequently treated with improper procedures (Figure 2B).

The following ways to fill this niche are proposed:

– Facilitating trainees' exposure to specialized multidisciplinary groups/clinics that care for patients with vascular anomalies, as they are the cornerstone of proper training.

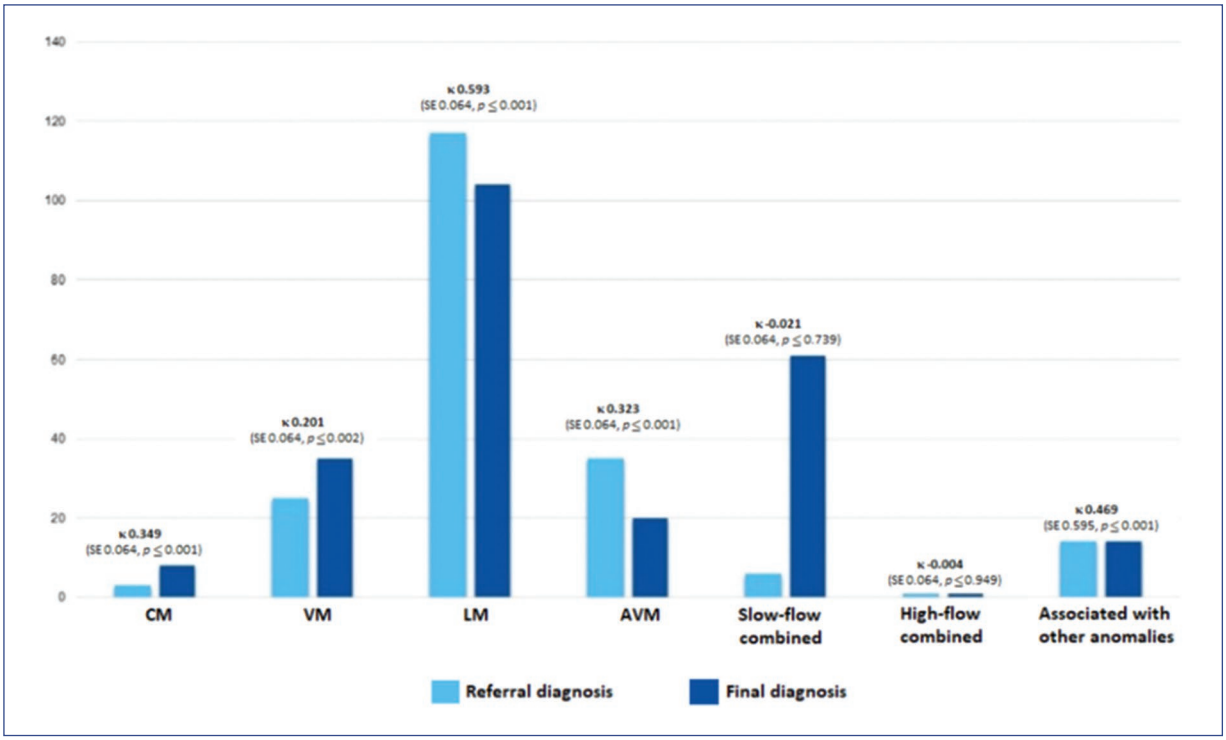

Figure 1. Fleiss kappa (κ) concordance analysis between referral and final diagnoses of patients with vascular malformations (VaM). AVM, arteriovenous malformations; CM, capillary malformations; LM, lymphatic malformations; SE, standard error; VM, venous malformations.

Figure 2. A. Patient with a venous malformation (VM) from birth on the lower lip that was diagnosed as a nevus. At 3 years of age, the lesion increased in size and volume and became painful. She was diagnosed with a hemangioma and treated with propranolol and topical corticosteroids for 6 months. Due to a lack of response, she was referred to the Vascular Anomalies Clinic (VAC), where she was successfully treated with polidocanol sclerotherapy. B. Patient with retroorbital venous-lymphatic malformations (VLM) observed at 2 years of age due to volume increase and proptosis after trauma. Computerized tomography findings suggested the probable diagnosis of alveolar rhabdomyosarcoma. A biopsy was performed, complicated by hemorrhage requiring drainage and tarsorrhaphy. Once diagnosed with VLM, the patient was referred to the VAC. Unfortunately, by this time, we found severe vision loss.

– Specialties involved in the care of these patients should advocate for this topic to be part of their conferences and journals.
– Development and distribution of specific guidelines or pathways, such as the European Vascular Anomalies (VASCA) Working Group[8].
– Inclusion of vascular anomalies as part of the dermatology curriculum for medical students.

Limitations of this study include the retrospective design and the limited number of patients with some types of VaM. However, we used the κ coefficient, considered the gold standard for measuring concordance by excluding random coincidences.

In conclusion, we found fair concordance between referral and final diagnoses of VaM. Continuing medical education strategies are necessary to improve adequate diagnoses and, therefore, the management of these patients.

Ethical disclosures

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

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

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

Conflicts of interest

The authors declare no conflicts of interest.

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CLINICAL CASE

Pigmented neurofibroma with hypertrichosis

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Abstract

Background: *Pigmented (or melanocytic) neurofibroma (PN) constitutes only 1% of cases and is considered a rare variant of neurofibroma containing melanin-producing cells. In addition, the association of PN with hypertrichosis is infrequent.* **Case report:** *We describe the case of an 8-year-old male with a neurofibromatosis type 1 (NF1) diagnosis, who presented a light brown hyperpigmented plaque, smooth and well-demarcated, and hypertrichosis on the left thigh. The skin biopsy showed characteristics of neurofibroma; however, in the deep portion of the lesion, melanin deposits positive for S100, Melan-A, and HMB45 were observed, thus establishing the diagnosis of pigmented neurofibroma.* **Conclusions:** *Although PN is a rare subtype of neurofibroma, it is considered a chronically progressive benign tumor containing melanin-producing cells. These lesions can appear alone or in association with neurofibromatosis. Since this is a tumor that can be confused with other skin lesions, biopsy analysis is essential to differentiate it from other pigmented skin tumors, such as melanocytic schwannoma, dermatofibrosarcoma protuberans, neurocristic hamartoma, or neuronevus. Surveillance is part of the treatment, and surgical resection is sometimes performed.*

Keywords: *Neurofibroma. Pigmented neurofibroma. Melanotic neurofibroma. Hypertrichosis. Latino. Case report.*

Neurofibroma pigmentado con hipertricosis

Resumen

Introducción: *El neurofibroma pigmentado (NP) o melanocítico constituye solamente el 1% de los casos y se considera como una variante rara del neurofibroma que contiene células productoras de melanina. Además, la asociación de NP con hipertricosis es muy rara.* **Caso clínico:** *Se describe el caso de un paciente de sexo masculino de 8 años 2 meses de edad con diagnóstico de neurofibromatosis tipo 1 (NF1), quien presentaba en la cara anterior del muslo izquierdo una placa hiperpigmentada de color café claro, bien delimitada y de consistencia suave, e hipertricosis. La biopsia de piel presentó cambios característicos de neurofibroma; sin embargo, en la porción profunda de la lesión se observaron depósitos de melanina positivos para S100, Melan-A y HMB45, con lo que se estableció el diagnóstico de neurofibroma pigmentado.* **Conclusiones:** *Aunque el NP es un subtipo raro del neurofibroma, se considera que es un tumor benigno de evolución crónica de células productoras de melanina. Estas lesiones aparecen en solitario o asociadas con neurofibromatosis. Dado que es un tumor que puede confundirse con otras lesiones cutáneas, es fundamental el análisis de la*

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biopsia para diferenciarlo de otros tumores cutáneos pigmentados, como el schwanoma melanocítico, dermatofibrosarcoma protuberans, hamartoma neurocrístico o neuronevus. La vigilancia es parte del tratamiento y, en ocasiones, se lleva a cabo la resección quirúrgica.

Palabras clave: *Neurofibroma. Neurofibroma pigmentado. Neurofibroma melanocítico. Hipertricosis. Latino. Reporte de caso.*

Introduction

Neurofibromas are benign peripheral nerve sheath tumors[1]. Pigmented neurofibroma (PN), also called melanocytic neurofibroma, is a rare subtype of neurofibroma that contains melanin-producing cells and constitutes only 1% of neurofibroma cases[2]. As other pigmented tumors share the same neuroectodermal origin, the clinical and pathologic diagnosis of these tumors is challenging. The occurrence of hypertrichosis in neurofibromas (including PN) is very rare[3]. Here, we present the case of PN associated with hypertrichosis in a schoolchild.

Clinical case

We describe the case of an 8-year-2-month-old male patient, native and resident of Oaxaca, Mexico, the only child of non-consanguineous parents. Family history: a father with NF1, normal perinatal data, uncomplicated pregnancy. Birth weight was 3130 g, height 49 cm, and head circumference 35 cm. Currently, the patient presents complete neurodevelopment for his age.

The patient has congenital pseudarthrosis of the left tibia and fibula, requiring osteotomy of the left tibia. In addition, he has right multicystic renal dysplasia, hydronephrosis, secondary arterial hypertension, and neurogenic bladder. Since the patient is a carrier of NF1, he is under multidisciplinary medical follow-up in a tertiary hospital in Mexico City.

At one year of age, his current condition began when he presented a localized dermatosis on the left lower extremity affecting the anterior aspect of the thigh and ipsilateral knee, consisting of a light brown hyperpigmented spot, well-demarcated and smooth in consistency. The lesion was asymptomatic, with slow and progressive growth after the patient's development. An increase in the volume of the area and the appearance of hair follicles (data compatible with hypertrichosis) on the spot's surface were observed at the age of 3 years (Figure 1). Due to the progression of the lesion (increase in volume, number, and diameter of hair follicles), we decided to perform a skin biopsy.

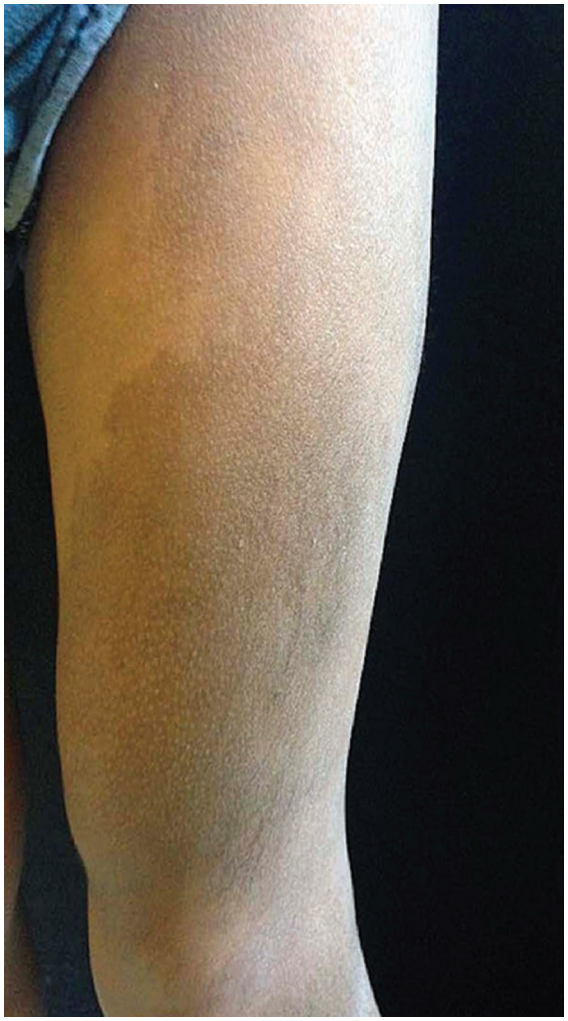

Figure 1. Neoformation with the appearance of a light brown hyperpigmented plaque and well demarcated with hypertrichosis (16 × 9 cm).

Skin biopsy showed an epidermis with stratum corneum in a basket network and flattening of the interpapillary processes. The superficial to mid-reticular dermis showed a proliferation of spindle cells with "italic" S-shaped nuclei intermingled with mast cells and concentrically arranged in a myxoid stroma (Figure 2). In the deep portion of the lesion, melanin deposits were found interspersed between the spindle cells, which stood out with the Fontana-Masson stain (Figure 3A).

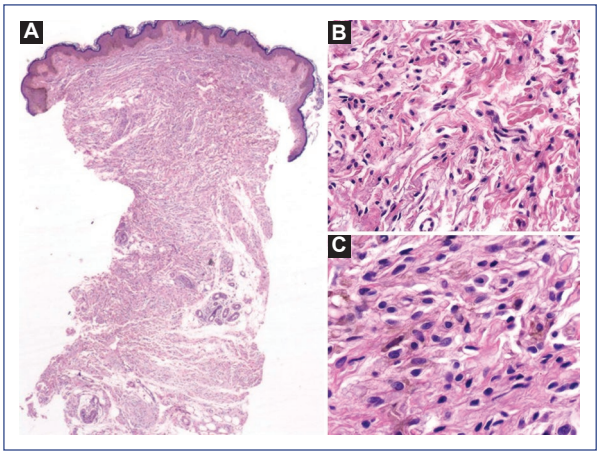

Figure 2. A: skin biopsy showing a diffuse spindle cell proliferation affecting the superficial, middle, and deep dermis, as well as adipose tissue. **B:** superficial portion of the lesion showing spindle cells with "italic" S-shaped nuclei intermixed with mast cells and arranged in a whirling pattern in a lax stroma. **C:** in the deep portion, more bulky ovoid cells with brown pigment deposits in their cytoplasm are identified.

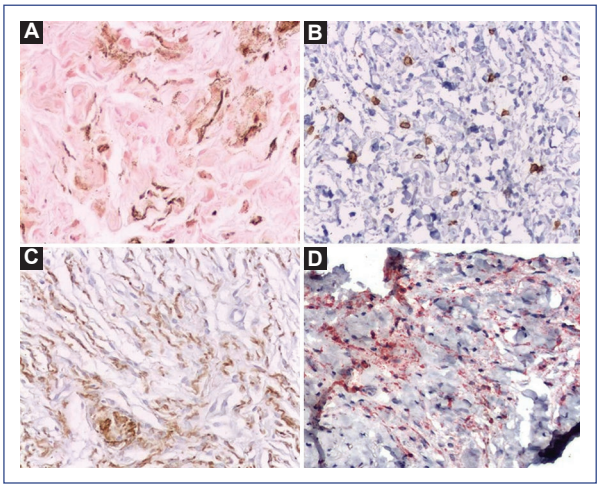

Figure 3. A: Fontana Masson stain positive for melanin in the cytoplasm of ovoid cells in deep dermis and in macrophages. **B:** CD117 labeling for plasma cells, which intercalate between the dendritic cells of the neurofibroma. **C:** S100 protein positive (brown) in Schwann cells of neurofibroma. **D:** Melan-A (in red) positive in melanin-producing spindle cells.

Immunohistochemistry showed CD117-positive mast cells (Figure 3B) and S100-positive spindle cells (Figure 3C). Immunohistochemical markers Melan-A and HMB45 showed some interspersed melanocytes, mainly in the deep portions of the lesion (Figure 3D). Intercalated structures were observed between spindle cells with immunolabeling for neurofilaments (Figure 4). On this basis, the anatomopathological diagnosis of PN was established. The patient continued with his multidisciplinary medical follow-up. Regarding the management of PN, it was decided to monitor the lesion every six months.

Discussion

PN is a cutaneous tumor that affects more females and predominates during the second and third decades of life, although some reports show an age range of 2 to 71 years[3,4]. These tumors can occur in isolation or be associated with NF1.

PN has been described more frequently in dark-skinned populations: in two series, 86% of patients were from Africa, Asia, or Latin America[3,5,6]. The most frequent topography of this pathology is the scalp[3,5]; other locations are the neck, hands, buttocks, thighs, and legs[6]. Morphologically, the lesions are tumors with no visible pigment in most cases. Occasionally, the lesions are accompanied by hyperpigmented spots with shades ranging from gray to brown and different pigment intensities. In a case series, Fetsch et al. observed that only 16% of the tumors investigated showed macroscopically detectable areas of pigmentation. The lesions had a rubbery consistency with poorly defined borders[2]. Moreover, a size range from 1 to 50 cm in diameter has been described[7]; some tumors appear as a single lesion, although two lesions have been identified in the same patient[6].

Furthermore, an association between hypertrichosis and neurofibroma is rare, especially in PN[2,3,8]. This lesion's mechanism for excessive hair growth has not been well established. Some authors consider that localized hypertrichosis may occur due to abnormal signals for follicular papilla elongation, including growth factors (epidermal bone growth factor, vascular endothelial growth factor, platelet-derived growth factor, and bone morphogenic protein) and a prolonged anagen phase of the hair cycle[3]. Other authors have established the possibility that localized acquired hypertrichosis may occur in areas of friction, trauma, or inflammation, suggesting that local factors may influence these growth mediators and determine the increase in the anagen phase[3].

Only five cases of PN associated with hypertrichosis have been published[2,3,8]. These tumors are usually accompanied by hyperpigmented spots with hypertrichosis on their surface and are lesions > 10 cm. In addition, the lesions appear early in life and progress gradually. Finally,

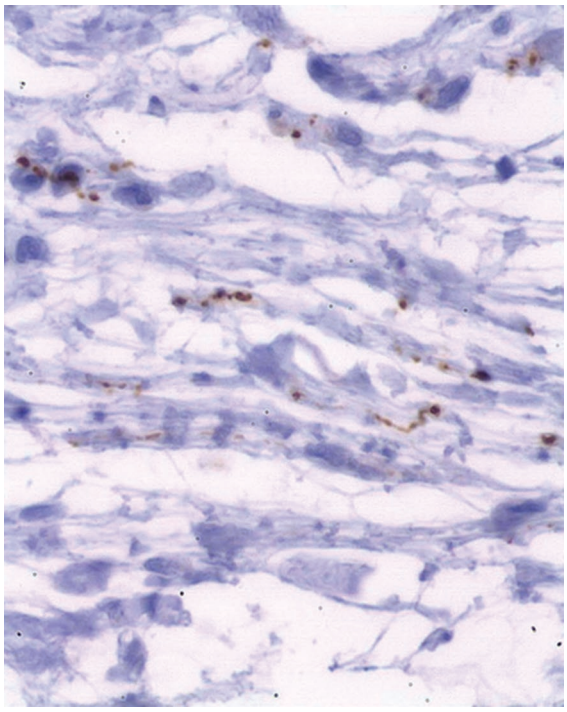

Figure 4. Positive immunolabeling for neurofilaments (in brown) characteristic of neurofibroma. The presence of these structures is essential for differential diagnosis with other pigmented neural tumors.

most PNs are part of the clinical spectrum of NF1, with neither sex nor age group predominance.

PN is an exophytic neoformation involving the dermis and subcutaneous cellular tissue, composed of fascicles of spindle or epithelioid cells distributed throughout the tumor, immersed in a stroma with collagen and matrix. Microscopically, PNs present the features of neurofibromas. Most cases show features of diffuse neurofibroma; others resemble the plexiform type, and in other cases, characteristics of both[4,6]. Occasionally, the spindle cells may be arranged in a storiform pattern[7]. Most lesions may contain abnormal nerve segments with disorganized Schwann cells and Wagner-Meissner corpuscles[6]. Other findings include increased mast cells and the occasional presence of randomly distributed multinucleated giant cells in the stroma[6].

PN is the only subtype of neurofibroma that contains melanin-producing cells that tend to be located in the deep dermis and subcutaneous cellular tissue; according to Motoi et al., this pattern may be a valuable tool to differentiate PN from other pigmented lesions[5]. The presence of melanin-producing cells may be due to the origin of melanocytes and Schwann cells, which is from neural crest cells[5,9]. To date, it has been debated whether the pigmented cells in this tumor are displaced melanocytes or Schwann cells with aberrant melanogenesis[6]. Detecting microphthalmia transcription factor (MITF) in the nuclei of PN tumor cells further supports the phenotypic relationship between melanocytes and melanin-producing Schwann cells, as this transcription factor is essential for melanocyte development and survival[10,11].

Melanin within phagocytes can be identified in different areas of the dermis and subcutaneous cellular tissue when stained with Fontana-Masson and Warthin Starry[12]. On immunolabeling, the tumor expresses S100 protein and melanin markers[4-6]: Melan-A, MITF (critical regulatory factor of melanogenesis), and HMB45. At times, these tumors are positive for tyrosinase and C-Met (involved in regulating melanogenesis)[5]. The characteristic immunohistochemistry of PN suggests that it is a single tumor showing differentiation towards mature melanin production (with mature melanocytes) but with apparently impaired synthesis capacity[5,6].

Fetsch et al. proposed some pathological diagnostic criteria for PN in their review: 1) mild histologic appearance to diffuse neurofibroma or a neurofibroma with combined histologic features of plexiform and diffuse; 2) immunolabeling to S-100 protein, HMB-45 antigen, and CD34[2,6].

PN can be confused with pigmented and hypertrophic tumors or masses. The primary differential diagnoses of this tumor are melanocytic schwannoma[13], pigmented dermatofibrosarcoma protuberans (Bednar's tumor)[14,15], cellular blue nevus[16,17], giant congenital melanocytic nevus with neuroid features[18,19], and cutaneous neurocristic hamartoma[20-23] (Table 1). To prevent doubts during diagnosis due to the clinical expression of PN, it is always advisable to take a biopsy of the lesion, whose anatomopathological characteristics may define the final diagnosis.

No standardized treatment for PN has been established. In some situations, partial resection of the tumor is necessary due to extra weight, limitations in daily activities, and cosmetic improvement. Surveillance is suggested, as some cases of PN present recurrence. No malignant transformation has been shown in any of these tumors, and follow-up data are insufficient to comment specifically on this issue[4,7]. Finally, there is no treatment to prevent the appearance of PN.

Most of the time, PN appears in individuals with a confirmed diagnosis of neurofibromatosis; therefore, patients already have a multidisciplinary medical follow-up of their genodermatosis and only need clinical observation of the PN. Surveillance or surgical management will be chosen depending on the tumor's evolution. When a PN appears spontaneously, other cutaneous

Table 1. Differential diagnoses to be considered in pigmented neurofibroma

Characteristics	Pigmented neurofibroma	Melanocytic schwannoma[13]	Dermatofibrosarcoma protuberans pigmentosum (Bednar's Tumor)[14,15]	Blue cellular nevus[16,17]	Cutaneous neurocristic hamartoma[18,19]	Giant congenital melanocytic nevus with neuroid features[20-23]
Origin	Peripheral nerve sheath: neuro-mesenchymal tissue; perineural, Schwann and melanin-producing cells	Peripheral nerve sheath consisting of Schwann cells	Fibrohistiocytic with dendritic cells	Dendritic melanocytic	Neuro-mesenchyme with fibrogenic, melanogenic and neurosustentacular differentiation	Melanoblasts: nevus cells and Shwann cells
Location	Hairy skin, neck and lower extremities	Axial region, nerve roots of the spinal cord, central and autonomic nervous system	Trunk, inguinal region and lower extremities	Buttocks in sacrococcygeal region, hairy skin, face and extremities	Head (in hairy skin) and trunk (thorax and back)	Trunk in bathing suit area and extremities.
Clinical manifestations	Hyperpigmented, poorly defined tumors of rubbery consistency	Solid mass with well-demarcated brown and/or black borders	Multinodular pigmented tumor firm to touch/Sclerotic or atrophic plaque	Dark blue neoformation with smooth dome-shaped surface	Focal alopecia Solitary neoformation of nodular appearance	Brown plaque with flat or mammillary surface, well-demarcated borders, hypertrichosis
Accompanying symptoms	Asymptomatic	Radicular pain, dysesthesias and progressive sensory-motor involvement.	Asymptomatic	Small painless lesions, large ones painful and ulcerating	Asymptomatic	Asymptomatic occasional pruritus
Cell phenotype	Spindle or epithelioid cells	Elongated cells some with epideloid appearance	Mesenchymal spindle cells	Pigmented dendritic melanocytes mixed with epitheloid cells	Nevomelanocytes, schwann cells, pigmented dendritic cells, spindle cells and fibroblasts	Neuroid and Schwan elements
Other histological data	Wagner-Meissner bodies, Schwann cells and mast cells	Psammoma bodies (40-50%) Laminated calcifications Mature adipocytes	Pigmented dendritic cells Verocay bodies	Cell islets may form digitate projections or bulbous expansion (dumbbell pattern)	Tactoid bodies Decrease in hair follicles	Elongated or thin melanocytes (type C) with fibrillar collagen structures resembling Meissner's corpuscles or Verocay's bodies
S-100	Positive	Positive	Negative	Positive	Positive	Positive
HMB45 and/or Melan-A	Positive	Positive	Negative	Positive	Positive	Positive
Other immunomarkers	MIFT, CD34	Vimentin, Leu7	CD34+, SMA, CD117, vimentin	SOX10, MART-1	CD34 and NSE	
Associations	Neurofibromatosis 1	Carney complex Recurrence, malignancy (10%) and metastasis capacity	Intermediate malignancy, high risk of recurrence		Possible transformation to malignant melanoma	Spina bifida, neurocutaneous melanosis and potential for malignant transformation

signs of NF1 (more than six café-au-lait spots, axillary or inguinal ephelides, and more neurofibromas)[24] should be sought. Patients should be referred to ophthalmology, neurology, orthopedics, cardiology, gastroenterology specialties, and genetics to determine whether their tumor is associated with NF1 or is found in isolation (solitary PN); this latter presentation is significantly rarer.

Currently, no preventive treatment is available to prevent the formation of these lesions; however, documenting them early on favors their close surveillance and timely therapeutic decision.

PN is a rare subtype of neurofibroma considered a benign tumor of unknown origin and chronic evolution that presents melanin-producing cells. Clinically, most patients show tumors without visible pigment, but some have hyperpigmentation, hypertrichosis, or both. These lesions appear solitary or associated with NF1. Histologically, their type is diffuse, although some have features of both types (diffuse and plexiform) and are accompanied by melanin-producing cells. As this tumor can be confused with other skin lesions, it is essential to take a biopsy. The histological, ultrastructural, and immunohistochemical findings will allow skin lesion diagnosis and differentiation from other pigmented skin tumors. In case of a new lesion, a multidisciplinary evaluation (Ophthalmology, Neurology, Genetics) should exclude neurofibromatosis. It is necessary to provide genetic counseling to the family upon genodermatosis confirmation. Treatment of PN consists of surveillance and, occasionally, surgical resection.

Ethical disclosures

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

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

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

Conflicts of interest

The authors declare no conflicts of interest.

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CLINICAL CASE

Extrarenal rhabdoid tumor of anterior mediastinal location

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Abstract

Background: *Rhabdoid tumors are malignant neoplasms of low prevalence, aggressive behavior, and high mortality. They were initially described as renal tumors, although tumors with the same histopathological and immunohistochemical characteristics have been discovered in other locations, mainly in the central nervous system. Few cases of mediastinal location have been reported internationally. This work aimed to describe the case of a mediastinal rhabdoid tumor.* **Case report:** *We describe the case of an 8-month-old male patient admitted to the pediatric department with dysphonia and laryngeal stridor progressing to severe respiratory distress. Contrast-enhanced computed tomography of the thorax showed a large mass with homogeneous soft tissue density, and smooth and well-defined borders, with suspicion of malignant neoplasm. Due to the oncological emergency compressing the airway, empirical chemotherapy was initiated. Subsequently, the patient underwent incomplete tumor resection due to its invasive nature. The pathology report showed morphology compatible with a rhabdoid tumor, which immunohistochemical and genetic studies corroborated. Chemotherapy and radiotherapy to the mediastinum were administered. However, the patient died three months after the initial treatment due to the aggressive behavior of the tumor.* **Conclusions:** *Rhabdoid tumors are aggressive and malignant entities difficult to control and have poor survival. Early diagnosis and aggressive treatment are required, although the 5-year survival does not exceed 40%. It is necessary to analyze and report more similar cases to establish specific treatment guidelines.*

Keywords: *Tumor. Rhabdoid. Mediastinum.*

Tumor rabdoide extrarrenal de localización mediastinal anterior

Resumen

Introducción: *Los tumores rabdoides son neoplasias malignas de baja prevalencia, con comportamiento agresivo y alta mortalidad. Inicialmente fueron descritos como renales, aunque posteriormente se han descrito tumores con las mismas características histopatológicas e inmunohistoquímicas en otros sitios, principalmente en el sistema nervioso central. Internacionalmente se han descrito pocos casos de localización mediastinal. El objetivo del presente trabajo fue describir el caso de un tumor rabdoide de localización mediastinal.* **Caso clínico:** *Se presenta el caso de un paciente de sexo masculino de 8 meses de edad que ingresó al servicio de pediatría con disfonía y estridor laríngeo que progresó a dificultad respiratoria severa. En la tomografía computarizada contrastada de tórax se observó una gran masa homogénea con densidad de tejidos*

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blandos, de bordes lisos y bien definidos, por lo que se sospechó una neoplasia maligna. Debido a la urgencia oncológica compresiva de la vía aérea se inició con un esquema empírico de quimioterapia. Posteriormente se sometió a resección tumoral incompleta por carácter invasor. El reporte de patología mostró morfología compatible con un tumor rabdoide, el cual se corroboró con estudios de inmunohistoquímica y genética. Se administró un esquema de quimioterapia y radioterapia al mediastino. Sin embargo, el paciente falleció a los 3 meses del inicio de tratamiento debido al comportamiento agresivo del tumor. **Conclusiones:** *Los tumores rabdoides son entidades agresivas y malignas de difícil control y con pobre supervivencia. A pesar de que se requiere un diagnóstico precoz y un tratamiento agresivo, no se ha logrado la supervivencia a 5 años mayor al 40%. Es necesario analizar una mayor cantidad de casos para establecer guías específicas de tratamiento.*

Palabras clave: *Tumor. Rabdoide. Mediastino.*

Introduction

Rhabdoid tumor, one of the most aggressive and lethal neoplasms in the pediatric population, mainly affects children under 3 years of age and is usually located in the kidney.

Although its localization outside the kidney is rare, a presentation called an atypical rhabdoid teratoid tumor is found in the central nervous system.

Other atypical locations have been described, such as the head, neck, thorax, mediastinum, liver, ileum, genitourinary tract, and retroperitoneum[1]. Most tumors contain biallelic somatic inactivation with mutations found in the *SMARCB1* gene, located on chromosome 22q11.2. Under normal conditions, this gene controls cell growth, division, and death; one copy is inherited from the mother and one from the father. However, the cells of patients with rhabdoid tumor predisposition syndrome carry one functional copy of *SMARCB1* and one altered copy. This change causes the gene to malfunction and thus results in the accelerated growth of malignant cells[2].

The clinical picture depends on the location and size of the tumor. The mediastinal presentation may be asymptomatic or show signs and symptoms such as cough, stridor, respiratory distress, and evidence of vascular compression, such as superior vena cava syndrome[3].

This type of tumor has a poor prognosis: in a series of 100 children diagnosed with extracranial rhabdoid tumor (2005 to 2014), overall survival at 3 years was only 38.4%[4].

Malignant tumors are among the leading causes of mortality in pediatric patients, highlighting the importance of ruling them out as part of oncologic emergencies. This report aims to inform pediatricians how such a common symptom as laryngeal stridor can be secondary to severe pathologies, as in this case, a rhabdoid tumor of infrequent presentation. We also aim to raise awareness in the medical community about the timely detection of tumors and the identification of patients with a genetic predisposition. We report the clinical findings and the diagnostic-therapeutic methodology used unsuccessfully, in this case, to continue research on this subject and establish prognostic factors since there are no standardized therapy nor study protocols to develop an adequate chemotherapy/radiotherapy scheme that allows a higher survival rate.

Clinical case

We describe the case of an 8-month-old male patient admitted to the emergency department with 2-week evolution of symptoms consisting of rhinorrhea, sporadic cough, dysphonia, laryngeal stridor when crying, and polypnea. A posteroanterior and lateral chest X-ray reported mediastinal widening with airway compression; an emergency simple contrast-enhanced chest CT scan showed asymmetric hemithorax due to less volume expansion on the right side, with trachea decreased in caliber displaced to the left and surrounded by a hypoattenuating image with soft tissue density. Distally, the trachea partially recovered its caliber at the level of the carina; the main bronchi were well pneumatized. We observed a large mass with homogeneous soft tissue density and smooth, well-defined borders (6.7 x 4.6 x 5.5 cm in its principal axes), showing poor predominantly peripheral enhancement and small central vessels when contrast was administered. The mass displaced and compressed the trachea and the cardiac silhouette, causing atelectasis with an air bronchogram in the pulmonary base on the same side. The contralateral lung parenchyma was normal. The cardiac profile was of standard shape and size, slightly displaced to the left (Figure 1).

Alpha-fetoprotein and human chorionic gonadotropin results were negative.

Empirical chemotherapy with vincristine (0.05 mg/kg/day) and doxorubicin (1 mg/kg/day) was initiated to reduce

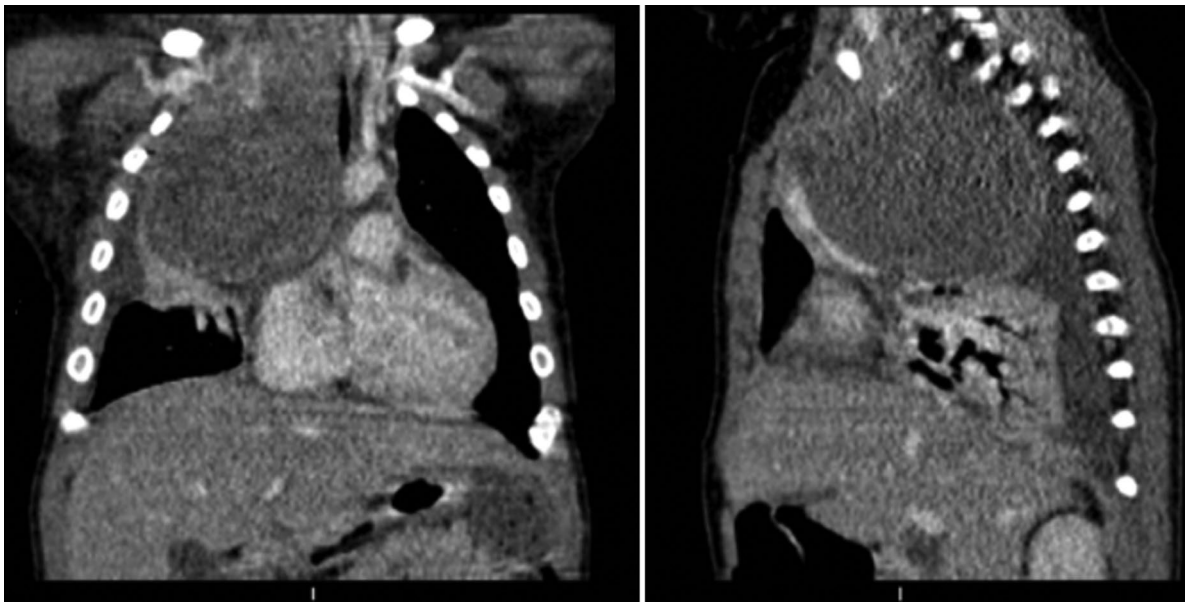

Figure 1. Initial computed axial tomography of the thorax in coronal and sagittal slices showed a solid mass of heterogeneous appearance, hypodense, displacing blood vessels and airway in the prevascular space, significantly reducing the tracheal caliber, right middle lobe atelectasis, and right pleural effusion.

tumor volume, and the patient was admitted to the Intensive Care Unit.

Two days after initiating chemotherapy, we found anterior cervical lymphadenopathy and data suggestive of superior vena cava syndrome. A total right pleural effusion was found with a chest X-ray (Figure 2), so emergency incomplete tumor resection and drainage of the pleural effusion by median sternotomy were performed without perioperative complications (Figure 3). The patient was extubated two days after surgery and was maintained on high-flow nasal prong therapy, which decreased to low-flow after 24 hours.

Bone marrow biopsy, aspirate, immunophenotyping, and karyotyping showed no neoplastic infiltration; urine alpha-fetoprotein, human chorionic gonadotropin, and catecholamine quantification tests were negative, excluding the presence of the most frequent mediastinal tumors.

The patient was discharged from the Intensive Care Unit three days later and admitted to the Pediatrics Service. A transthoracic Doppler echocardiogram reported a pedunculated mass (5 x 6 cm) located at the arrival of the superior vena cava to the right atrium, thus concluding tumor infiltration to great vessels and right atrium.

After ten days of stay in the pediatrics department, the patient presented an intense crying crisis

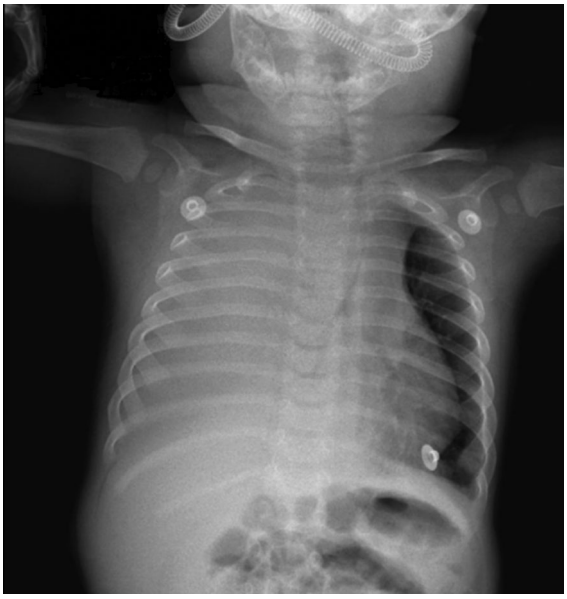

Figure 2. Chest X-ray before surgery. Right pleural effusion.

associated with stridor, severe respiratory distress, and significant desaturation, for which he was readmitted to the Intensive Care Unit, requiring high-flow ventilation. Subsequently, the patient presented bradycardia and severe desaturation with progression to mechanical

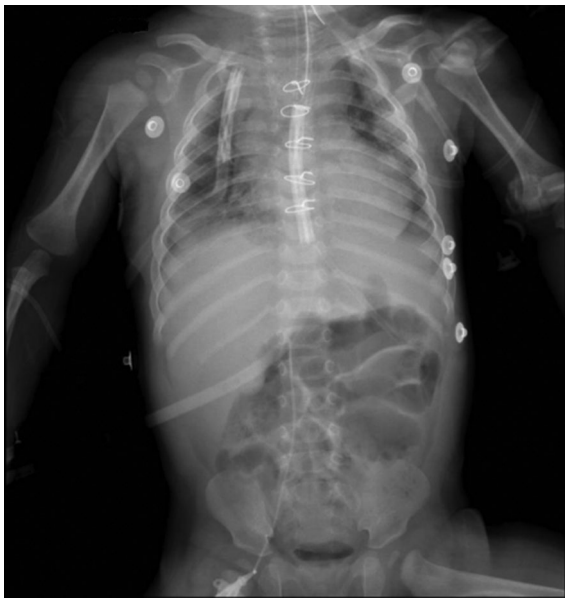

Figure 3. Chest X-ray after surgery. Presence of pleural drainage and residual tumor.

ventilation. Sedation and advanced resuscitation maneuvers were required.

The control radiography showed right basal pneumonia, suspected right diaphragmatic paralysis, and a mediastinal mass with airway obstruction. Bronchoscopy showed dynamic occlusion of 40% of the airway at the tracheal level; tracheomalacia was diagnosed.

The pathology report showed a poorly differentiated malignant neoplasm with abundant tumor necrosis and recent hemorrhage, with infiltration of adjacent soft tissues. It was classified as an extrarenal rhabdoid tumor with SALL4+, CMYC+, CKAE1/AE33+, GLIPICAN 3+, INI1-, and a proliferation index of 70%.

An antineoplastic regimen was initiated based on carboplatin (19 mg/kg/day, single dose), ifosfamide (1800 mg/m^{2}SC/day, days 1-3), and etoposide (3.3 mg/kg/day, days 1-3). Adequate tumor volume reduction was observed, and invasive mechanical ventilation was successfully withdrawn. He was discharged from the service and continued with chemotherapy according to the high-dose protocol of the European Rhabdoid Registry (EU-RHAB) for six cycles[5].

A genetic study by microsatellite technique showed *SMARCB1* gene loss, which confirmed the diagnosis of extrarenal rhabdoid tumor. Treatment was complemented with radiotherapy at a dose of 50.4 Gy in 28 fractions with concomitant weekly radiosensitizing vincristine with apparent good initial clinical evolution. However, during radiotherapy, the patient presented tumor progression data, so it was necessary to start a second-line VOIT (vincristine, irinotecan, temozolomide) scheme without a favorable response to treatment. The patient died 85 days after diagnosis and treatment.

Discussion

The present case report describes an 8-month-old male patient with an initial clinical picture of laryngeal stridor and respiratory distress. The clinical picture at admission initially suggested laryngotracheitis; however, differential diagnoses had to be considered, among which extrinsic compression of the airway and neoplasms were possible etiologies. Airway compression was initially diagnosed by chest X-ray and later delimited by computed tomography. This etiology explains the cause of the failure of the initial treatment with racemic epinephrine. Subsequently, the presence of the most frequent mediastinal tumors was ruled out through biochemical data. Finally, a more specific study protocol was initiated for less frequent pathologies, treating the patient initially with empirical chemotherapy. Once the tumor type was morphologically identified, treatment for this type of tumor was initiated based on the EU-RHAB. The diagnosis was corroborated by pathology and immunohistochemistry studies, determining the loss of the *SMARCB1* gene. Despite adhering to the management guidelines established by EU-RHAB, the prognosis was as unfavorable as the international statistics at 3 months of follow-up under oncologic and surgical treatment.

Rhabdoid tumors are highly aggressive and lethal in the pediatric population. These tumors mainly affect children under 3 years of age, with a higher frequency in males[3]. The present case was an 8-month-old infant, an age group in which biallelic somatic inactivation secondary to the *SMARCB1* gene mutation occurs and less frequently the *SMARCA4* gene mutation. A predisposition due to a germline mutation may exist[6-9].

Few cases of rhabdoid tumors located in the mediastinum have been described. One case was reported in Mexico of a female patient with chronic upper respiratory tract infection diagnosed by immunohistochemistry and treated with radiotherapy and chemotherapy based on cyclophosphamide, carboplatin, and etoposide[9,10]. In the case described here, a *SMARCB1* gene mutation was identified by a microsatellite genetic study, which supported *SMARCB1* or *INI-1* gene deficiency. The *SMARCA4* gene mutation has a higher ratio in hereditary transmission from one of the healthy

parents unaffected by the mutation, whereas the *SMARCB1* gene exceptionally presents in this form.

Rhabdoid tumors are mainly located in the kidney; the most frequent extrarenal location is in the central nervous system (up to 50% in the cerebellum), although it can infrequently occur in the head and neck, paravertebral muscles, liver, bladder, mediastinum, retroperitoneum, and heart.

The clinical presentation will depend on the location. The mediastinal presentation usually includes chest pain, dyspnea, cough, variable respiratory distress, and constitutional symptoms such as weight loss and generalized weakness[3]. Some cases even include superior vena cava syndrome or compression of the airway or great vessels due to mass effect or direct invasion of the tumor[1,11,12]. As we observed in this case, the patient showed an atypical extrarenal location in the mediastinum that started with respiratory symptoms due to the mass effect of the tumor.

In the case of neurological localization, this tumor has been described with initial presentation of subarachnoid and intraventricular hemorrhage[13], and even acute hydrocephalus[14] and *de novo* spinal cord presentations. There are also reports of cases in which it is difficult to distinguish between this type of tumor and other more frequent tumors or other pathologies. Differential diagnoses have been reported with yolk sac type tumors, neurofibromatosis type 2, and hydrops fetalis with a metastatic presentation of the tumor to the placenta during pregnancy[15-17].

On computed tomography, the mediastinal tumor appears as a large heterogeneous mass that commonly presents displacement of the heart and mediastinal structures[3]; it also tends to infiltrate blood vessels, the airway, and adjacent structures. In this case, we described a tumor that caused a significant displacement of vessels and the airway, and infiltration of the superior vena cava and right atrium, which made it unresectable due to its invasive characteristics. The definitive diagnosis was made with histopathological and immunohistochemical studies, identifying the representative morphological characteristics in addition to the *SMARCB1*- or *SMARCA4*- gene mutations[1,3,6,9].

Histologically, this type of tumor is classified into the following main groups: conventional-type tumors, the most common with the typical description; atypical teratoid/rhabdoid-type tumors, with myxoid matrix pattern, basophilic or with mucopolysaccharides, and small cell-type tumors, without rhabdoid cells, with small, round cells and scarce cytoplasm[18]. This case corresponds to the conventional type.

The mediastinal rhabdoid tumors usually present in advanced stages when it has become unresectable, as in this case. Approximately 20% of patients will have disseminated disease at the time of diagnosis. Survival curves have shown a survival rate of 31-38% at 3 years and 15-36% at 5 years[1,7,13].

The suggested treatment described by the European Rhabdoid Registry is based on high-dose chemotherapy. It is also necessary to evaluate which patients will benefit from the adjuvant use of radiotherapy, depending on the presentation, manifestations, time of diagnosis, and prevention of complications inherent to oncologic treatment. There is no registry of prognostic factors for survival, so it is not yet possible to determine which patients will benefit from each scheme established by the European registry.

A strength of this case report is that all the information on the tumor was available; however, the diagnosis was difficult due to the low incidence of this neoplasm. Additionally, no diagnostic and treatment protocol for this type of non-neurological extrarenal tumor has been reported in the literature. Moreover, it is essential to remember that oncologic emergencies also cause respiratory distress. Therefore, it is vital to identify them promptly.

Mediastinal extrarenal rhabdoid tumor is a rare, very aggressive tumor with a poor prognosis. Although an early diagnosis and aggressive treatment are required, a 5-year survival > 40% has not been possible to exceed[10]. For this reason, it is necessary to study more cases to achieve specific treatment guidelines.

This paper describes the case of an 8-month-old patient with infiltration of large vessels and extrinsic compression of the airway, with an initial presentation of laryngeal stridor and severe respiratory distress. An exhaustive study was necessary to reach the clinical, imaging, surgical, histopathological, immunohistochemical, and genetic diagnoses. The multidisciplinary medical team administered thorough treatment. This is the first documented case in Mexico of a rhabdoid tumor with *SMARCB1* gene loss detected by microsatellites, immunohistochemistry, and pathology.

Ethical disclosures

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

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

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

Conflicts of interest

The authors declare no conflicts of interest.

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Fibrodysplasia ossificans progressiva in a 3-year-old female patient

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Abstract

Background: *Fibrodysplasia ossificans progressiva (FOP) is a rare autosomal dominant disease affecting connective tissue, primarily caused by de novo mutations of the ACVR1 gene. FOP is a disease with congenital malformations of the toes and heterotopic ossification in characteristic patterns that progresses with flare-ups and remissions. Cumulative damage results in disability and, eventually, death. This report aimed to describe a case of FOP to highlight the importance of early diagnosis of this rare condition.* **Case report:** *We describe the case of a 3-year-old female diagnosed with congenital hallux valgus, who initially presented with soft tissue tumors, predominantly in the neck and chest, with partial remission. Multiple diagnostic tests were performed, including biopsies and magnetic resonance imaging, with nonspecific results. We observed ossification of the biceps brachii muscle during evolution. The molecular genetic study found a heterozygous ACVR1 gene mutation that confirmed FOP.* **Conclusions:** *Knowledge of this rare disease by pediatricians is critical for an early diagnosis and for avoiding unnecessary invasive procedures that may promote disease progression. In case of clinical suspicion, performing an early molecular study is suggested to detect ACVR1 gene mutations. The treatment of FOP is symptomatic and focused on maintaining physical function and family support.*

Keywords: *Myositis ossificans. ACVR1 gene. Hallux valgus.*

Fibrodisplasia osificante progresiva en una paciente de 3 años

Resumen

Introducción: *La fibrodisplasia osificante progresiva (FOP) es una enfermedad autosómica dominante rara que afecta el tejido conectivo, cuya causa principal son mutaciones de novo del gen ACVR1. Se trata de una enfermedad con malformaciones congénitas de los primeros ortejos y osificación heterotópica en patrones característicos que progresa en empujes y remisiones. El daño acumulativo provoca discapacidad y, eventualmente, la muerte. El objetivo de este trabajo fue describir un caso de FOP para favorecer el diagnóstico precoz de esta enfermedad infrecuente.* **Caso clínico:** *Se describe el caso de una paciente de 3 años, portadora de hallux valgus congénito, que inicialmente presentó tumoraciones dolorosas de tejidos blandos, de predominio en cuello y tórax, con remisión parcial de las mismas. Se realizaron múltiples pruebas diagnósticas, incluyendo biopsias e imágenes de resonancia magnética con resultados inespecíficos. En la evolución se*

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observó osificación de músculo bíceps braquial. El estudio genético molecular encontró una mutación del gen ACVR1 en heterocigosis que confirmó el diagnóstico de FOP. **Conclusiones:** *El conocimiento de esta enfermedad por los pediatras es clave para realizar un diagnóstico precoz y evitar procedimientos invasivos innecesarios que pueden promover la progresión de la enfermedad. Ante la sospecha clínica, se sugiere realizar tempranamente el estudio molecular para detectar mutaciones del gen ACVR1. El tratamiento de la FOP es sintomático, centrado en el mantenimiento de la función física y el apoyo familiar.*

Palabras clave: *Miositis osificante. Gen ACVR1. Hallux valgus.*

Introduction

Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disease, with an estimated incidence of 0.6-1.3 per million individuals[1], characterized by progressive heterotopic endochondral ossification and congenital malformations of the great toes[2]. It is included in the Online Mendelian Inheritance in Man (OMIM) registry under number 135100[3].

FOP evolves in flare-ups that produce new areas of ossification, leading to progressive motor disability and death, mainly due to restrictive respiratory complications[4]. It is an autosomal dominant disease caused by heterozygous mutations in the *ACVR1* gene encoding the activin receptor IA (ACVR1/ALK2), a protein in the bone morphogenetic signaling pathway[5].

Although several drugs are used to treat this pathology, there is yet to be a treatment with proven clinical efficacy[1].

We report the case of a female patient diagnosed with FOP at the age of 3 years. The objective is to inform the case of a rare disease that generated diagnostic difficulties. Knowledge of this entity can avoid unnecessary paraclinical evaluations that can be iatrogenic and favor disease progression.

Clinical case

We describe the case of a 3-year-old female patient with good growth and development, healthy parents, and two healthy siblings. The patient showed congenital bilateral *hallux valgus* and had a complete immunization scheme. The patient was evaluated for presenting 2-week evolution of multiple painful cervical tumors in both jugular-carotid regions, predominantly on the right side. She showed fever in the first two days of onset of the disease, remaining in apyrexia afterward. No symptoms of intercurrent infection and general compromise were further observed.

Initially, the tumors were of firm-elastic consistency, 3 cm in diameter, and adhered to the muscular planes. They were accompanied by erythema of the overlying skin, which disappeared during evolution, acquiring a stony consistency. Lymphoganglionic examination revealed multiple mobile adenomegalies in jugular-carotid, submaxillary, axillary, inguinal, and abdominal regions; a painful pole of the spleen was palpated. On admission, the sternocleidomastoid and trapezius muscles had a stony consistency, generating painful torticollis (Figure 1).

During the 2-week hospital stay, tumors with similar characteristics were detected in other regions related to muscular structures: posterior cervical region, trapezius muscles, right subscapular region, and left paravertebral level (Figure 2). The rest of the physical examination showed no alterations.

An anatomopathological study and imaging follow-up of the lesions by ultrasound and magnetic resonance imaging (MRI) were performed. Malignancy and ossification were excluded. The rest of the complementary studies showed no alterations.

During outpatient follow-up after discharge, the patient presented partial regression of the tumors that motivated the initial consultation and similar lesions in the pectoral region, right dorsum, and abdominal wall.

Clinical and functional improvement occurred after initiating treatment with prednisolone at 2 mg/kg. However, the symptomatology returned when this dose was reduced. After five months of evolution, the patient presented pain and limitation of movement. The trapezius and sternocleidomastoid muscles, biceps, and triceps of the right upper limb showed a stony consistency, as well as at the biopsy sample extraction sites. Plain radiography of the right upper limb showed calcification of the right biceps brachii muscle (Figure 3).

The presence of muscular calcifications, in addition to the reevaluation in the diagnostic reasoning of congenital *hallux valgus*—interpreted until now as an isolated morphological alteration—allowed the establishment of the clinical diagnosis of FOP.

The molecular genetic study found *ACVR1*:c.617G>A (p.Arg206His) in heterozygosis, confirming the clinical diagnosis.

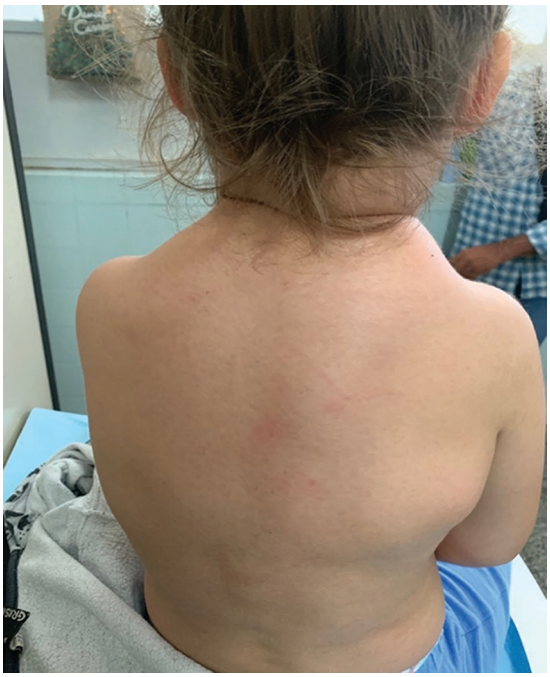

Figure 1. Hypertrophy of sternocleidomastoid and trapezius muscles.

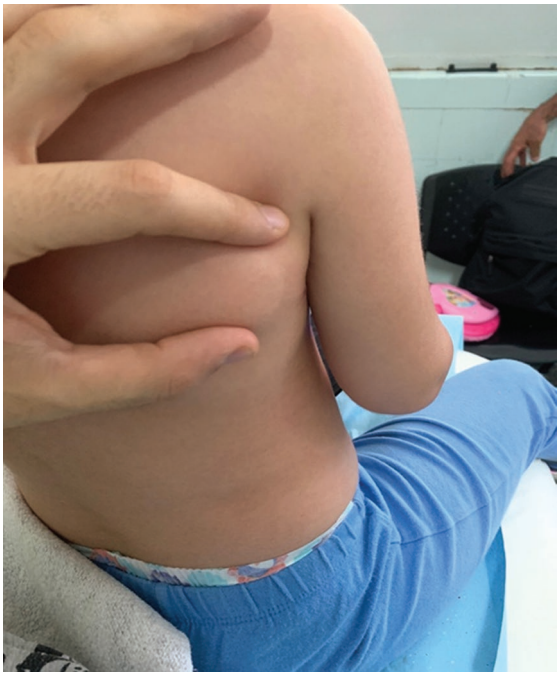

Figure 2. Tumor in the right subscapular region.

Discussion

This present case is the second case of FOP reported in Uruguay[6]. It is one of the so-called "ultra-rare" diseases, with an estimated incidence of 0.6-1.3 per million individuals. Diagnosis is clinical and confirmed by molecular studies1.4. No sex predominance has been established.

This autosomal dominant disease is caused by gain-of-function mutations in the *ACVR1* gene, located on chromosome 2q23-24. More than 95% of patients have the missense mutation c.617G > A (p.Arg206His), as this patient[5].

The *ACVR1* gene encodes for the activin receptor type IA, a membrane protein member of the family of intercellular signaling protein receptors called bone morphogenetic proteins (BMP) type I[5,7]. The p.Arg206His mutation, which consists of changing the amino acid arginine to histidine at position 206, resides in a domain critical for regulating this protein called the GS (glycine-serine) domain. This change causes a gain of function, leading to constitutive or ligand-independent deregulated activation, which explains its dominant expression. This mutation modifies the folding of the protein at the binding site of another protein (FKBP12) with inhibitory activity on *ACVR1*. The inability to be inactivated by its negative regulator generates constitutive activity of the receptor encoded by *ACVR1*. The consequent dysregulation of the BMP signaling pathway would lead to aberrant cartilage production from mesenchymal cells[8].

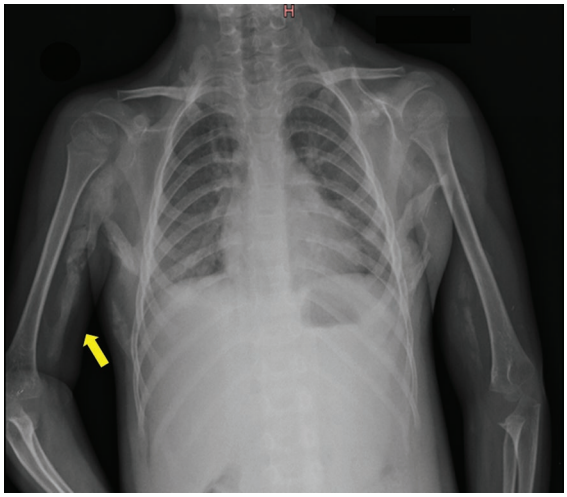

Figure 3. Radiographic evidence of ossification of the biceps brachii muscle.

Morphological alterations of the distal bones of the limbs are one aspect of the disease. Other recurrent mutations in this gene (p.Gly328Arg, p.Gly328Trp, and

p.Gly328Glu) are associated with characteristic limb alterations that may be mistaken for amniotic flange disruptions or type B brachydactyly. The penetrance of gain-of-function mutations in the *ACVR1* gene is estimated to be complete, as no cases with these mutations or their clinical expression have been reported[5]. As in most dominant diseases, wide phenotypic variability can be observed, and other genes and environmental factors likely modulate the presentation of the disease[5].

As we propose, most cases are sporadic, arising from a *de novo* mutation, since none of the parents have elements suggestive of this condition[1].

Two clinical elements classically define FOP: malformations of the great toe and progressive heterotopic endochondral ossification in characteristic anatomical patterns. Patients with FOP present as healthy neonates, except for the malformation of the great toe, which is present in all affected individuals, as observed in this case[2,4,9].

Initially, this patient presented tumors of firm-elastic consistency in the neck, with adherence to muscular planes. This observation led to other diagnoses, including hemato-oncologic causes, usually one of the most frequent initial approaches[10]. Initial imaging studies showed no calcifications, which generated diagnostic confusion. Current evidence demonstrates that the development of heterotopic ossification occurs after soft tissue inflammation[4,11]. Routine biochemical studies are usually normal, as observed in this patient. To date, no specific biomarkers have been identified[1].

Hallux valgus in the pediatric age group is usually acquired during infancy and childhood; it is infrequently congenital, as in this case[12]. Although congenital malformations of the great toes are a constant feature of FOP, their presence is not pathognomonic[1,2]. In addition, it is possible to observe other alterations that this patient did not present, such as malformation of the thumbs, clinodactyly, tibial osteochondromas, and wide and short femoral necks[1,5].

Affected patients develop episodic flare-ups of pain and soft tissue inflammation. Some episodes remit spontaneously, but in most of them, the soft connective tissues are transformed into bone tissue by endochondral ossification, leading progressively to permanent immobility. In addition, minor trauma, such as intramuscular immunizations, dental anesthesia, muscle fatigue, hematomas, falls, and infections, can trigger new flare-ups[1,4].

As observed in this patient, heterotopic endochondral ossification progresses following anatomical and temporal patterns that mimic the patterns of bone formation in the normal human embryo. It initially occurs in the dorsal, axial, cranial, and proximal regions of the body and is subsequently seen in the ventral, appendicular, caudal, and distal regions. Some skeletal muscles are unaffected, including the diaphragm, tongue, and extraocular muscles. Cardiac and smooth muscle tissues are also unaffected[5,13].

Most patients require assistance with activities of daily living in the early stages. Mandibular involvement is usually followed by significant malnutrition. A frequent cause of death in affected patients is progressive cardiorespiratory failure due to thoracic insufficiency syndrome, which results in the inability of the thorax to achieve normal ventilation. The median age at death is 40 years[13,14].

There is currently no definitive medical treatment for FOP. Therefore, management consists of supportive care. Since this is a chronic disease with a significant impact on quality of life, it is recommended that the care of patients with FOP be multidisciplinary[1,15].

High doses of glucocorticoids have shown efficacy in the early treatment of flare-ups affecting the major joints, mandible, and submandibular region[1,4]. They also help prevent flare-ups after trauma and surgery, decreasing the probability of heterotopic ossification in the affected sites[1,16]. The administration is suggested in the first 24 hours of the outbreak, at a daily dose of 2 mg/kg/day, for no more than 4 days. This patient received corticosteroids and presented a good initial response.

Nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, mast cell stabilizers, and anti-leukotrienes are helpful in pain management[17]. Other drugs, such as bisphosphonates and imatinib, are not routinely used but may contribute to managing difficult-to-control flare-ups[18].

New therapies are being investigated, including palovarotene derived from retinoic acid. This drug reduced the percentage of FOP patients who developed heterotopic ossification and is currently in a phase 3 study[19].

Surgical interventions to remove heterotopic bone tissue result in reactive bone regrowth, as observed at the biopsy specimen extraction sites in this patient, and are therefore contraindicated[1,10].

Preventive measures aimed at reducing flare-ups and subsequent ossification are essential. Patients with FOP should have prophylactic dental control, excluding mandibular anesthetic blocks. There is consensus on avoiding vaccination and intramuscular administration during flare-ups. Administration of vaccines with diphtheria, pertussis, and tetanus components, which are associated with a higher incidence of flare-ups, is not

routinely recommended[20]. For the same reason, muscle fatigue should be limited, and falls and respiratory infections should be prevented[1,10].

In conclusion, FOP is a sporadic disease often underdiagnosed, especially in its early stages. If clinical suspicion exists, early molecular testing is suggested to detect the most frequent mutations of the *ACVR1* gene. Current management of FOP consists mainly of symptomatic treatment, maintenance of physical function, and family support.

Ethical disclosures

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

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

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

Conflicts of interest

The authors declare no conflicts of interests.

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CARTA AL EDITOR

Prurigo solar y su asociación con el HLA-DR4 (DRB1*0407)

*Solar prurigo and its association with HLA-DR4 (DRB1*0407)*

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Sr. Editor:

Al ser una enfermedad relativamente común en nuestro medio, el prurigo solar (PS) o prurigo actínico ameritó la publicación de una amplia serie: 50 niños habitantes de la Ciudad de México atendidos en el Hospital General de México, étnicamente mestizos o indígenas y de bajo nivel socio-económico, 25 de sexo masculino, de 10 meses a 14 años de edad (media de edad de 8 años y mediana de 11.8 años)[1]. Estos niños fueron diagnosticados de acuerdo con criterios ampliamente aceptados[2]: 15 de ellos también presentaron la afección labial documentada como queilitis folicular, ya que al microscopio se observaron folículos linfoides bien conformados[3]. Alrededor del 50% (26/50) desarrollaron conjuntivitis (característica en esta enfermedad), misma que también ha sido bien documentada en nuestra población (Figura 1)[4].

Algunos años después de esta publicación, se dio la posibilidad de finalizar un estudio sobre la asociación entre el PS y los antígenos principales de histocompatibilidad (HLA). Se encontró que, en todos los pacientes, el HLA-DR4 (DRB1*0407) se encontraba presente.

La asociación con el HLA-DR4 (DRB1*0407) es compatible con el hecho de que el PS es una enfermedad peculiar en Latinoamérica, donde una gran proporción de la población es indígena o mestiza y comparte un antecedente racial que predispone a reaccionar anormalmente a la luz solar, en particular a la luz ultravioleta de onda media (UVB), la luz ultravioleta de onda larga (UVA) y a la luz visible. Algunos factores, como la dieta pobre en proteínas, también han sido estudiados como factores asociados[5].

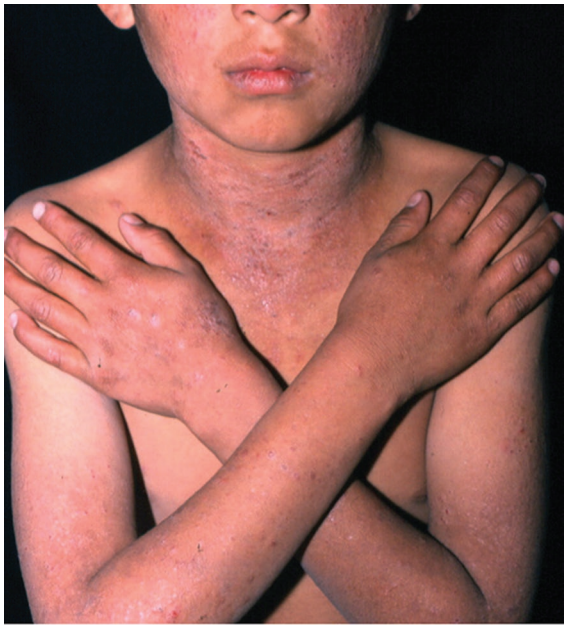

Figura 1. Presentación clínica clásica del prurigo solar: pápulas en todo estadio evolutivo situadas en zonas expuestas a la luz solar, con queilitis y conjuntivitis (no visible en esta imagen).

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El PS fue descrito en México en 1959[1,2]. Desde entonces, un gran número de investigaciones han sido desarrolladas por colegas mexicanos y latinoamericanos. Actualmente es un motivo aún frecuente de consulta y representa el decimocuarto lugar, con 1.3% de todos los niños atendidos en la Clínica de Dermatología Pediátrica de nuestro hospital[1].

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado. Los autores han obtenido el consentimiento informado de los pacientes y/o sujetos referidos en el artículo. Este documento obra en poder del autor de correspondencia.

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Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

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IN MEMORIAM

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El Dr. Velásquez Forero falleció el 5 de agosto de 2022 en la Ciudad de México. Originario de Colombia, cursó la carrera de Medicina en la Universidad Nacional de Colombia, en Santa Fe de Bogotá, donde se recibió como médico cirujano en 1959. Posteriormente se trasladó a los Estados Unidos de América para estudiar la especialidad de Anatomía Patológica en el Penrose Hospital, Colorado Springs, Colorado, y en la Universidad, en el Research and Educational Hospital, en Chicago, Illinois. Después, estuvo como *Associate Research Fellow* en el Departamento de Patología Renal del Michael Reese Hospital de Chicago y estudió la especialidad de Nefropatología bajo la dirección del Dr. Conrad L. Pirani.

Posteriormente, se trasladó a la Ciudad de México, donde se asentó definitivamente. Aquí formó una muy estimada familia que tuve el gusto de conocer, ya que el Dr. Velásquez Forero fue mi mentor. En buena medida, el me introdujo a la Patología, a la par de la influencia del Dr. Jorge Fernández Diez y del Dr. Héctor Payán.

Una vez en México, el Dr. Velásquez Forero cursó la Maestría y el Doctorado en Ciencias Médicas por la Universidad Autónoma Metropolitana. Su carrera académica fue larga y productiva: fue encargado del Departamento de Patología Quirúrgica en el Instituto Nacional de la Nutrición Salvador Zubirán de 1969 a 1971; jefe del Departamento de Anatomía Patológica en el Hospital Juárez de México de 1999 a 2000; consultante de Patología Renal del Departamento de Patología en el Centro Médico Nacional 20 de Noviembre de 1976 a 2000, entre otros encargos. El último de ellos fue el de jefe del Laboratorio de Metabolismo Mineral Óseo en el Hospital Infantil de México Federico Gómez.

En este laboratorio desarrolló las siguientes líneas de investigación:

- Actividad de la prostaglandina E1 sobre el calcitriol
- Osteodistrofias renales en niños
- Histomorfometría ósea en modelos experimentales y en enfermedades pediátricas
- Litiasis renal en niños
- Establecimiento de los valores de referencia de la biopsia ósea metabólica en adolescentes

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– Evaluación del metabolismo óseo pre y post-trasplante renal en niños y adolescentesComo resultado de estas líneas de investigación, y otras desarrolladas previamente, dirigió 14 tesis de posgrado, escribió más de 90 artículos sobre la fisiología del riñón y, últimamente, sobre las alteraciones del metabolismo mineral óseo, enfermedades del riñón y valores normativos de la biopsia ósea en niños mexicanos, registró dos patentes, publicó un libro y doce capítulos en otros libros. Fue organizador de varios cursos nacionales e internacionales sobre metabolismo óseo y participó en múltiples congresos nacionales e internacionales. Su actividad como docente fue amplia en varios ámbitos y su curiosidad lo llevó a entrenarse en diversos campos.

Recibió numerosas distinciones entre las que destacan las siguientes: Miembro Honorario de la Sociedad Colombiana de Nefrología (3 de agosto de 1973); reconocimiento por su dedicación a la investigación otorgado por el Centro Hospitalario 20 de Noviembre (1981); Socio Fundador de la Asociación Mexicana de Metabolismo Óseo y Mineral A. C; Miembro del Comité Organizador del IX Congreso de la Sociedad Internacional de Histomorfometría Ósea en Edimburgo, Escocia (7 al 10 de abril de 2002). Recibió el premio a la investigación científica como investigador D del Sistema Nacional de Investigadores, Secretaría de Salud (2002 a 2003). También obtuvo la Medalla al Mérito Universitario por haber obtenido las calificaciones más altas en el programa de Doctorado en Ciencias Biológicas de la UAM (diciembre de 2006).

Finalmente, he de señalar que el Dr. Velásquez Forero fue una persona generosa, siempre dispuesto a colaborar, un excelente anfitrión y con un particular sentido del humor que a menudo matizaba con decires colombianos. Además de sus intereses profesionales, destacaba su gran vocación por la cultura y las artes, particularmente por la pintura. Su esposa, Ana Gloria Martín del Campo, ha publicado libros de poesía. Su hija Roxana es directora del Museo de Artes de San Diego California, y sus otros cuatro hijos son todos profesionistas destacados. Fue sin duda un gran ser humano y un gran patólogo a quien vamos a extrañar.