HEARING LOSS AND VASCULAR CHANGES OF RETINA ASSOCIATED TO NEONATAL POLYCYTHEMIA – REPORT OF 02 CASES

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3. **CONFLICT OF INTERESTS:**

The authors declare no conflict of interests.

ABSTRACT

Objective: To report two newborn cases, one with retinal vascular changes and both with sensorineural hearing loss, which development factor could be neonatal polycythemia. **Case Description**. Case 01. A full-term newborn, without signs of perinatal asphyxia, developed symptomatic polycythemia on the second day of life and was treated with parenteral hydration. After 02 days, it developed retinal occlusion of the left vein and failed hearing screening test, which persisted in subsequent evaluations. Case 02. A full-term newborn, without signs of perinatal asphyxia, developed symptomatic polycythemia on the second day of life, treated with parenteral hydration. Neonatal hearing screening was normal, however, when repeated after three months, it developed sensorineural hearing loss in the left ear. **Comments:** Neonatal polycythemia is characterized by elevated levels of hemoglobin (above 22g/dL) and hematocrit (above 65%). Most affected newborns are asymptomatic. Simptoms may be secondary to hyperviscosity, which reduces blood flow and impair tissue oxigenation. There could be an association between neonatal polycythemia and retinal vascular changes or hearing loss, in which the reduction of blood flow secondary to hyperviscosity can be critical tissue with high oxygen demand. Retinal vascular changes due to neonatal polycythemia are rare, and there are no case reports of hearing loss associated to this condition. The main causes associated with retinal occlusion of the retinal vein were not found in case 01. Furthermore, the main causes related to neonatal hearing loss, including congenital infections and significant neonatal jaundice, was not present in the two cases of sensorineural hearing loss.

Key words: Neonatal diseases, Polycythemia, Hearing loss, Central Retinal Vein.

INTRODUCTION

Neonatal polycythemia (NP) is characterized by an increase in erythrocyte mass in newborns (NB), marked by elevated hemoglobin and hematocrit levels equal to or above 22 g/dL and 65%, respectively[1]. The global prevalence of NP ranges from 2% to 15%, and it can reach up to 44% in neonatal intensive care units (NICUs)[2]. The main risk factors for NP include conditions associated with chronic fetal hypoxia due to placental vascular insufficiency, such as hypertensive disorders of pregnancy[3], maternal smoking[4], small-for-gestational-age newborns or intrauterine growth restriction (IUGR)[2,4], gestational diabetes mellitus[5], Down syndrome[6], and delayed cord clamping[7]. In most cases, multiple risk factors are associated.

Hematocrit is the primary determinant of blood viscosity in newborns[6]. Secondary hyperviscosity caused by polycythemia reduces tissue blood flow, impairing oxygenation[7]. Most affected newborns are asymptomatic, but common symptoms include tremors, lethargy, vomiting, and feeding difficulties[1,6]. Rarely, cyanosis, apnea, or seizures may occur[6].

Central retinal vein occlusion (CRVO) is a rare condition in the neonatal period. Any situation promoting venous thrombus formation and subsequent obstruction of blood flow could lead to retinal damage[8]. CRVO is clinically diagnosed via fundoscopy, which reveals tortuous and dilated retinal veins and retinal hemorrhages[8]. Hearing loss (HL) in the neonatal period is primarily associated with risk factors such as hyperbilirubinemia, aminoglycoside use for more than five days, perinatal asphyxia, intrauterine infections, e.g., cytomegalovirus (CMV), and bacterial meningoencephalitis[9]. To date, no studies have linked hearing loss to NP.

Neonatal polycythemia, retinal vein occlusion, and hearing loss may be associated due to hyperviscosity mechanisms. Blood flow obstruction in highly specialized tissues with high oxygen demands, such as retinal and cochlear cells, is particularly critical[6].

This study aims to report two cases of newborns delivered at Maternidade Climério de Oliveira (Salvador, Bahia) in 2021, one presenting vascular retinal alterations and both with sensorineural hearing

loss (SNHL), with neonatal polycythemia being a common associated factor. This case report was approved by Research Ethics Committee by the protocol number 83805324.3.0000.5543.

CASE 1

E.S.J., female, born to a 36-year-old mother (G3P2A0) with chronic hypertension and preeclampsia, who denied maternal smoking. Prenatal serologies for CMV, toxoplasmosis, syphilis, hepatitis B and C, HIV, and HTLV were unremarkable. The newborn was delivered via cesarean section at 39 weeks and 4 days of gestation, weighing 3774g, appropriate for gestational age. The newborn was vigorous at birth with no signs of perinatal asphyxia, and did not require neonatal resuscitation. The umbilical cord was clamped within the first minute of life. APGAR scores were 7 and 8 at the 1st and 5th minutes, respectively.

In the first few postpartum hours, the newborn exhibited poor sucking and regurgitation, requiring gastric lavage and subsequent improvement under observation in the rooming-in-care unit. Symptoms persisted until 30 hours of life, when the newborn appeared plethoric, jaundiced, lethargic, and mildly dehydrated. Laboratory tests showed hemoglobin at 24.8 g/dL and hematocrit at 75%. Hyperbilirubinemia was present, but did not require phototherapy and showed no ABO/Rh incompatibility. White blood cell count, reticulocyte count, electrolytes, calcium, and phosphorus levels were normal (Table 01).

The newborn was transferred to the NICU and initiated on intravenous hydration, showing improvements in alertness and breastfeeding over five days and achieving effective polycythemia control. Fundoscopy performed on fourth day of life revealed venous engorgement in both eyes and retinal vein occlusion in the left eye (Figure 01). Bilateral failure in otoacoustic emissions (OAE) testing was identified at six days of life. Other neonatal screening tests were normal. Urinary PCR for CMV was negative.

By day eight, the newborn developed hypotonia, hyporesponsiveness, and brief generalized tonic-clonic seizures. Clinical and laboratory investigations, including cerebrospinal fluid analysis and culture, led

to a diagnosis of ischemic stroke at 17 days of life (Figure 02). Follow-up fundoscopy at 18 days confirmed venous occlusion and diffuse arteriolar narrowing. Sensorineural hearing loss (SNHL) was confirmed via auditory brainstem response (ABR) testing at 24 days. After seizure control, exclusive breastfeeding training, and clinical improvement, the infant was discharged home at 30 days of life.

CASE 2

R.O.A., male, born to a 30-year-old mother (G3P2A0) with gestational hypertension and severe preeclampsia, who denied maternal smoking. First-trimester maternal serologies showed positive IgG and IgM for herpes (HSV) without any history of genital lesions before or during pregnancy. Prenatal serologies for toxoplasmosis, CMV, hepatitis B and C, syphilis, HIV, and HTLV were unremarkable. The newborn was delivered via cesarean section at 38 weeks and 1 day of gestation, weighing 3420 g, appropriate for gestational age. APGAR scores were 8 and 8 at the 1st and 5th minutes, respectively.

Within 12 hours postpartum, the newborn exhibited weak sucking, regurgitation, and significant weight loss (~8%). Gastric lavage and formula supplementation were initiated. At 36 hours, jaundice developed without other symptoms. Laboratory tests showed hemoglobin at 23.7 g/dL and hematocrit at 70%. Hyperbilirubinemia was present but did not require phototherapy and showed no ABO/Rh incompatibility (Table 01).

The newborn was transferred to the NICU for intravenous hydration, showing improved alertness and breastfeeding. However, rebound polycythemia occurred less than 24 hours after stopping IV hydration. Parenteral hydration was restarted, followed by gradual weaning once hematocrit stabilized.

Routine ultrasound and neonatal screenings, including auditory screening, were normal. Fundoscopy on day two revealed retinal hemorrhages consistent with delivery trauma. Audiological follow-up at four months of life revealed severe combined hearing loss on OAE and ABR testing, findings confirmed at six months of life. Neurological evaluation found normal neuropsychomotor development, except difficulty localizing sounds.

DISCUSSION

The increase in fetal erythropoiesis is enhanced in situations of chronic intrauterine hypoxia, such as in hypertensive disorders of pregnancy[4,6]. Thus, given the prenatal and birth history of both neonates, the common risk factor, preeclampsia, could be the triggering factor for neonatal polycythemia.

Delayed umbilical cord clamping is the most common cause of polycythemia in healthy full-term neonates. Although this practice rarely results in clinically significant PN, the chances of occurrence increase when clamping exceeds three minutes or when umbilical cord milking is performed; in such cases, the neonate's blood volume may increase by up to 30%[6,10]. Therefore, although both neonates in this report underwent delayed cord clamping, it was performed within the first minute of life, making it unlikely as the etiology of polycythemia.

The potential repercussions of PN on cochlear and retinal microvasculature remain poorly studied. The relationship between blood viscosity and hematocrit is linear up to 60%; it becomes exponential when the hematocrit exceeds 65%[4]. Studies show reduced blood flow in small-caliber vessels in polycythemic neonates, as well as increased platelet-endothelial interaction. The combination of these factors could favor thrombus formation, worsening tissue perfusion[8]. Hyperviscosity associated with NP could explain the cerebral ischemia presented by the patient in case 01. Unlike cerebral ischemia secondary to intrauterine growth restriction (IUGR), perinatal asphyxia, or complex congenital heart diseases—which typically present within the first three days of life[12,13]—the neonate in case 01 developed late-onset cerebral ischemia. A factor strongly associated with late-onset cerebral ischemia is bacterial meningitis[13]; however, the neonate in case 01 had normal cerebrospinal fluid biochemistry, cytology, and culture.

Neonatal retinal vascular occlusions (RVOs) are rare and are usually secondary to sepsis or multiple intracranial hemorrhages[14,15]—causes that were ruled out in case 01. Therefore, hyperviscosity secondary to polycythemia could have caused retinal occlusion and cerebral ischemia in case 01.

Regarding hearing loss, case-control studies have shown that this condition could be associated with cerebral ischemia[16]. However, in Case 01, hearing loss preceded the ischemic event, and in case 02, there were no clinical findings or imaging compatible with cerebral ischemia.

Congenital infections are among the most critical causes to be evaluated in cases of hearing loss[17], particularly cytomegalovirus (CMV) infection, which was ruled out in Case 01. In Case 02, since the neonate had a normal first hearing screening and no symptoms compatible with congenital CMV infection during hospitalization, there was no indication for investigation during the neonatal period. However, most cases of congenital CMV infection are asymptomatic, and hearing loss associated with this infection may manifest later[17]. In these situations, the determination of the etiology of hearing loss becomes even more complex due to potential confounding factors[17].

To date, there is no precise diagnostic method to differentiate between congenital and acquired CMV infection in cases of post-neonatal hearing loss. A probabilistic diagnosis can be made through serial paired serology evaluations of the mother-infant pair[17]. In Case 02, the CMV serology follow-up is unknown, making it difficult to definitively rule out congenital CMV infection as the cause of hearing loss.

Unlike CMV, there is no proven association between herpes simplex virus (HSV) infection and hearing loss[18]. A systematic review observed that neonates affected by disseminated HSV infection, presenting with significant clinical severity, also had sensorineural hearing loss[18]. However, the authors did not confirm a causal relationship due to the presence of other risk factors, such as prematurity and neonatal asphyxia. The same study found no cases of hearing loss in individuals with asymptomatic HSV infection. Finally, the epidemiology of other viruses in the TORCHS group has changed significantly over time, with only congenital CMV currently associated with hearing loss[9]. In Case 02, maternal serology for HSV was more likely a false positive since the mother had no compatible lesions at any time before or during pregnancy. The neonate's stable clinical course throughout hospitalization makes hearing loss due to HSV highly unlikely.

The relationship between neonatal hyperbilirubinemia and hearing loss is well established[19]. Case-control studies have demonstrated this association at significant bilirubin levels, especially above 20 mg/dL, in cases of autoimmune hemolytic anemia or those treated with exchange transfusion[20]. However, for hyperbilirubinemia below phototherapy levels, the association with hearing loss has not been confirmed. Although both neonates in this case report developed late-onset neonatal jaundice, neither case was secondary to hemolytic anemia, nor did they require phototherapy[19].

Hyperviscosity due to polycythemia could be the factor associated with hearing loss in both cases due to the obstruction of blood flow and subsequent hypoxia, given the high metabolic demands of the inner ear, which requires an intact vascular network. Experimental studies have shown that reduced blood flow and consequent tissue hypoxia in the inner ear could induce anaerobic cellular metabolism, the formation of free radicals, and inflammatory cytokines capable of damaging adhesion molecules essential for the integrity of the blood-labyrinth barrier—a crucial structure for the proper functioning of the inner ear[20].

During the neonatal period, retinal and auditory complications associated with PN have been rare or go unnoticed, especially since hematocrit levels between 65% and 70% are often managed expectantly if there are no clinical symptoms. Moreover, polycythemic neonates, unless they present with other risk factors, are generally not subjected to fundoscopy or repeated hearing screening following the diagnosis of this clinical condition, potentially leading to underestimation of these diagnoses in the neonatal population.

CONCLUSION

NP is a multifactorial and relatively common condition, particularly in NICUs. While most newborns remain asymptomatic, the hyperviscosity associated with NP can lead to severe complications, particularly in tissues with high oxygen demands, such as the retina and cochlea. These cases highlight the need for further research to explore the potential relationship between NP, vascular retinal changes, and hearing loss.

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FIGURES

Figure 01. Fundoscopy of the right eye (a and b) and the left eye (c and d). Increased tortuosity and venous engorgement in both eyes (*). Occlusion of the central retinal vein (black arrow).

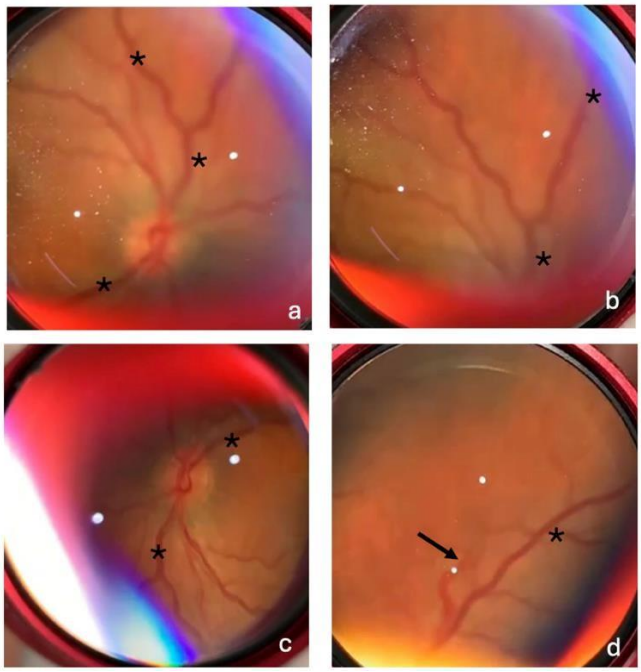

Figure 02. Nuclear Magnetic Resonance Images. (a) Axial T2-weighted section and (b) Coronal T2-weighted section, showing ischemic lesions in both frontoparietal lobes, bilateral (*). (c) and (d) Axial diffusion-weighted section, showing diffusion restriction at both frontoparietal lobes (white arrow).

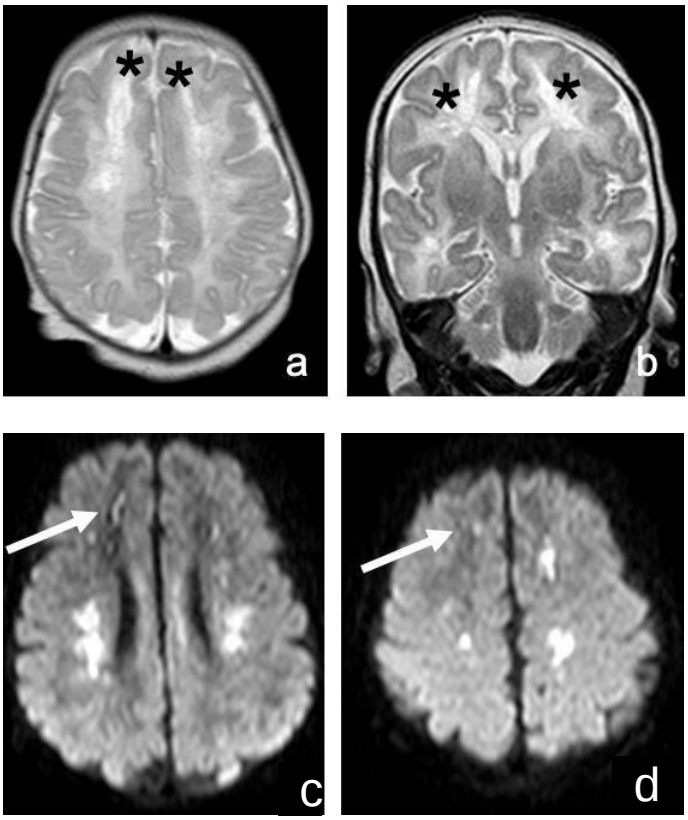

Table 01. Case description, symptoms of neonatal polycythemia, treatment, polycythemia management, control exams after initial treatment, fundoscopy and auditory screening description, complications and outcome.

Case	Symptoms of neonatal polycythemia	Diagnostic exams at neonatal polycythemia presentation	Polycythemia management	Control exams after treatment	Fundoscopy	Auditory screening	Complications	Outcome
01 **Maternal complications** Chronic hypertension Preeclampsia **Gestational age** 39 4/7 **Birth weight** 3774g (p88) **APGAR score** 7/8 **Delivery** Cesarian section	Poor feeding Regurgitation Hypoactivity Neonatal jaundice	Hb 24,8g/dL Hct 75% Ret 1,4% Plt 185 mil/mm3 WBC 8,950cel/mm3 CRP 1,2 Serum glucose 92mg/dL TB 6,9 (IB 6,3) mg/dL Na 147 K 5,7 Ca 9,4 P 5,7 Mg 2,1	Venous hydration for 05 days	Hb 19,2 g/dL Hct 59% (at seven days of live)	Bilateral venous engorgement and occlusion of the venous branch in the left eye (at four days of life) Diffuse arteriolar narrowing and occlusion of the venous branch in the left eye (at eleven days of life)	OAE (at six days of life): Bilateral failure. ABR (at eleven days of life): Moderate hearing loss on the right and mild on the left.	At eight day of life: Generalizesd tonic-clonic seizures Acute ischemic stroke	Discharge home at 30 days of life.
02 **Maternal complications** Gestational hypertension Severe preeclampsia **Gestational age** 38 1/7 **Birth weight** 3240g (p77) **APGAR score** 8/8 **Delivery**	Poor feeding Regurgitation Hypoactivity Neonatal jaundice	Hb 24g/dL Hct 72% Ret1,1% Plt 123 mil WBC 9,815cel/mm3 Serum glucose 61mg/dL TB 8,6 (IB 8,2) mg/dL	Venous hydration for 04 days	Hb 20,7 g/dL Hct 62,6% (at six days of life)	Retinal hemorrhage	OEA (at four days of life): normal	At eight day of life: Rebound polycythemia: Hb 24g/dL Hct 72%	Discharge home at 12 days of life. OAE and ABR at four and six months of life: severe combined hearing loss.

Cesarian section								

Legend: **Hb:** hemoglobin **Hct:** hematocrit **WBC:** White blood cell count **Plt:** Platelets **CRP:** C Reactive protein.**TB:** total bilirubin. **IB:** indirect bilirrubin. **Retic:** reticulocyte count. **Na:** sodium **K:** potassium **Ca:** calcium. **P:** phosphorus **Mg:** magnesium. **OAE:** otoacustic emissions. **ABR:** auditory brainstem response.

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