

Case Report**NEONATAL INTRAVENTRICULAR HEMORRHAGE PRESENTING AS PYREXIA OF NEWBORN:
A CASE REPORT**Maha Taranish^{1,2*}, Saima Almani^{1,2}, Olubukunola Adesanya^{1,2}

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Abstract: Background Temperature instability is a relatively common presenting symptom in a Neonatal Intensive Care Unit (NICU) with sepsis being one of the major etiologies that need to be ruled out. However, an important differential diagnosis is a central fever. Many cases of Intracranial Hemorrhage/Intraventricular Hemorrhage (ICH/IVH) present with temperature dysregulation with no other clear associated symptoms, and cranial imaging for early identification and treatment of ICH/IVH is crucial.

Case report A 3-day-old male born at 33 weeks and four days of gestation who was admitted to the neonatal critical care unit due to prematurity and respiratory distress was noted to be febrile during the fourth hospital day. The septic screen was negative, and the patient continued to spike fever while on broad-spectrum antimicrobial treatment. Due to an unexplained drop in his hematocrit, cranial ultrasound was done, and grade III IVH was identified. The patient continued to improve clinically, but the exact etiology of his IVH was not identified. His fever resolved without interventions, and his IVH continued to decrease in size. Serial cranial imaging was done in NICU, and no neurosurgical interventions were warranted. He was referred to neurosurgery and neurology and followed in the infant's high-risk clinic.

Discussion Sepsis is the top of differentials when managing a newborn infant in NICU. However, we must always keep our minds open to other differentials, including central hyperthermia. Extreme prematurity is a major risk factor for ICH/IVH in the neonatal period; nonetheless, other risk factors are identified, and many cases of ICH/IVH had no identified causative factor or even risk factors.

Conclusion Identifying clinical presentation and risk factors associated with ICH and IVH in NICU patients is crucial for early diagnosis and offers appropriate management. A high index of suspicion is required to promptly diagnose ICH/IVH resulting in central fever and avoid unnecessary workup and treatment.

Keywords: Intraventricular hemorrhage, intracranial hemorrhage, prematurity, hyperpyrexia

INTRODUCTION Elevated temperature and its instability are a relatively common presenting symptom in a Neonatal Intensive Care Unit (NICU) with sepsis being one of the major etiologies that need to be ruled out. However, an important differential diagnosis is a central fever. Compared with fevers caused by infections, central fever occurs earlier and lasts longer with higher temperatures. It

might happen in neonates with subarachnoid hemorrhages, intraventricular hemorrhages, or traumatic brain injuries but occurs less commonly in ischemic stroke. Many cases of Intracranial Hemorrhage/Intraventricular Hemorrhage (ICH/IVH) present with temperature dysregulation with no other clear associated symptoms. Cranial imaging for early identification and treatment of ICH/IVH is crucial.

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CASE PRESENTATION A 3-day-old male newborn in our neonatal intensive care unit presented with a fever that started on the fourth day of life. The infant was born virginally to a 21-year-old G1P1 mother with limited prenatal care. Pregnancy was complicated by diet-controlled gestational diabetes (A1 type), preeclampsia with severe features, elevated MAFP (Maternal serum alpha-fetoprotein) prenatally, for which the mother declined amniocentesis, and noninvasive prenatal testing (NIPT) and fetal ultrasound was within normal limits, newborn's mother had a car collision two days before delivery described as a low-speed impact with no maternal complaints or injuries on physical examination and no evidence of acute trauma. Other pregnancy histories include maternal overweight, with excessive weight gain in pregnancy.

Perinatally, the mother received two doses of betamethasone before delivery, insulin drip, Magnesium sulfate drip, hydralazine, labetalol, Nifedipine, Misoprostol, Oxytocin drip, and epidural anesthesia.

Mother tested negative for Group B streptococcus, and artificial rupture of membranes was done 13 hours and 16 minutes prior to delivery with clear amniotic fluid. There was no reported maternal fever or fetal tachycardia during delivery. Apgar score was 6 and 7 at 1 and 5 minutes after delivery, respectively, and birth weight was 2460 grams. Cord PH was 7.19. The newborn received positive pressure ventilation and oxygen support at 3 and 5 minutes of life due to irregular breathing and grunting. The baby was then transferred to the neonatal intensive care unit (NICU) due to prematurity, sepsis risk, and need for respiratory support. His physical exam after delivery was unremarkable, apart from grunting and caput succedaneum. The newborn was then started on CPAP (Continuous Positive Airway Pressure), received nothing by mouth (NPO), kept on intravenous fluid, and started later enteral feeding via nasogastric tube.

Initial septic workup at admission was reassuring; hence, the baby was not started on empiric antibiotics. He had neonatal hyperbilirubinemia that improved with phototherapy.

The newborn started to spike fever during the fourth day of admission (3 days of age); a complete septic workup was done, including cerebrospinal fluids analysis, and the newborn was started on ampicillin, gentamicin, and acyclovir. Septic workup was largely negative; however, a

significant drop of hemoglobin and hematocrit was noted in his CBC, with initial hemoglobin and hematocrit upon admission being 62 and 20.7, respectively, and dropped down to 46 and 16.9. A head ultrasound was performed on the newborn due to concerns regarding intracranial/intraventricular hemorrhage (IVH) being the cause of the sudden drop of hemoglobin, and it showed a large grade III right IVH and a small grade III left IVH.

The patient's IVH was monitored with serial head ultrasound images; his pyrexia soon abated. All cultures during that time returned negative, including urine, blood, and cerebrospinal fluid cultures.

The infant continued to improve clinically. He was successfully weaned to room air on the 12th day of life, all feedings were oral by the 20th day of life, and he was eventually discharged home after 24 days in NICU. Last HUS showed "small bilateral IVH with significant ventriculomegaly." He was referred to follow-up with neurosurgery and the infants' high-risk clinic. The etiology of the patient's IVH remains undetermined. However, we think it could be related to maternal trauma from a motor vehicle accident before delivery, which she encountered two days before delivery.

Patient follow-up and management after discharge

A pediatric neurosurgeon and neurologist followed up on the infant. A brain MRI was done during the follow-up and showed "mild hydrocephalus, with sequelae of prior IVH. No acute abnormalities were noted. The infant was referred to ECI, but he was noted to be growing and developing well. Given his clinical and imaging improvement, no further interventions were deemed necessary.

DISCUSSION Intraventricular hemorrhage (IVH) is a major complication of prematurity. IVH typically initiates in the germinal matrix due to the intrinsic fragility of the germinal matrix and vasculature and the disturbance in cerebral blood flow [1]. IVH in the neonatal period ranges from silent bleeding to extended bleeding into the ventricles or parenchyma. This event commonly occurs in preterm infants, especially those under 32 weeks of gestation and infants with very low birth weight [2].

Focal and generalized seizure appears in two-thirds of neonates with IVH, especially in the first 48 hours of birth [3]. Other less common manifestations include flaccidity, loss of pupillary reaction, loss of extraocular movements,

respiratory abnormalities, coma, jitteriness, irritability, vomiting, shrill cry, full fontanel, gaze palsy, central facial weakness, opisthotonic posturing, fever or hypothermia, hypo- or hyperglycemia, decreased lower extremity tone, neck flexor hypotonia, head lag, and brisk reflexes [2]. The type and severity of IVH-related symptoms depend on the size of the hemorrhage, the location of bleeding, damage to the surrounding tissues, and other underlying predisposing factors of bleeding. However, IVH in approximately 25 to 50% has remained asymptomatic and only can be discovered through imaging procedures [2].

Many patients in intensive care units have fevers from noninfectious causes, but this is often treated as infectious fever. Fever of central origin was first described in the journal "Brain by Erickson" in 1939 [4]. The unjustified use of antibiotics adds to the increased cost of treatment and the emergence of resistant strains, contributing to additional morbidity. Since fever has a detrimental impact on the recovery of the acutely injured brain [5-10] and contributes to an increase in the length of stay in the NICU, a timely and accurate diagnosis of the cause of fever in the NICU is imperative.

IVH is thought to elevate the temperature set point in the hypothalamus by direct damage to the thermoregulatory centers in the preoptic region, stimulation of prostaglandin production, or decreased inhibitory

feedback from the lower midbrain which suppresses thermogenesis [4].

Although it is a well-recognized sequela, the clinical course of fever following intracerebral hemorrhage (ICH) and intraventricular hemorrhage (IVH) with or without ICH has yet to be well-studied. Patients with fever following either ICH or IVH routinely undergo extensive testing only to conclude that the fever is "central" in origin.

There is not enough data available previously to report fever due to intraventricular hemorrhage. However, IVH should be included in the differential diagnosis of fever in premature infants in the NICU.

A common practice in neonatal ICUs is ruling out sepsis in premature babies with fever. Our patient had a relatively low risk for sepsis, given a reassuring initial partial septic workup, GBS-negative maternal screen, and lack of prolonged rupture of membranes. However, he had a fever while on broad-spectrum antibiotics and antiviral, which raised concerns regarding the noninfectious origin of his fever (see Figure 1). Though he did not meet the criteria for qualifying for a routine IVH/ICH screen, a head ultrasound was done, given the likelihood of central fever and the sudden drop in his hemoglobin and hematocrit, which showed IVH (Figure 2).

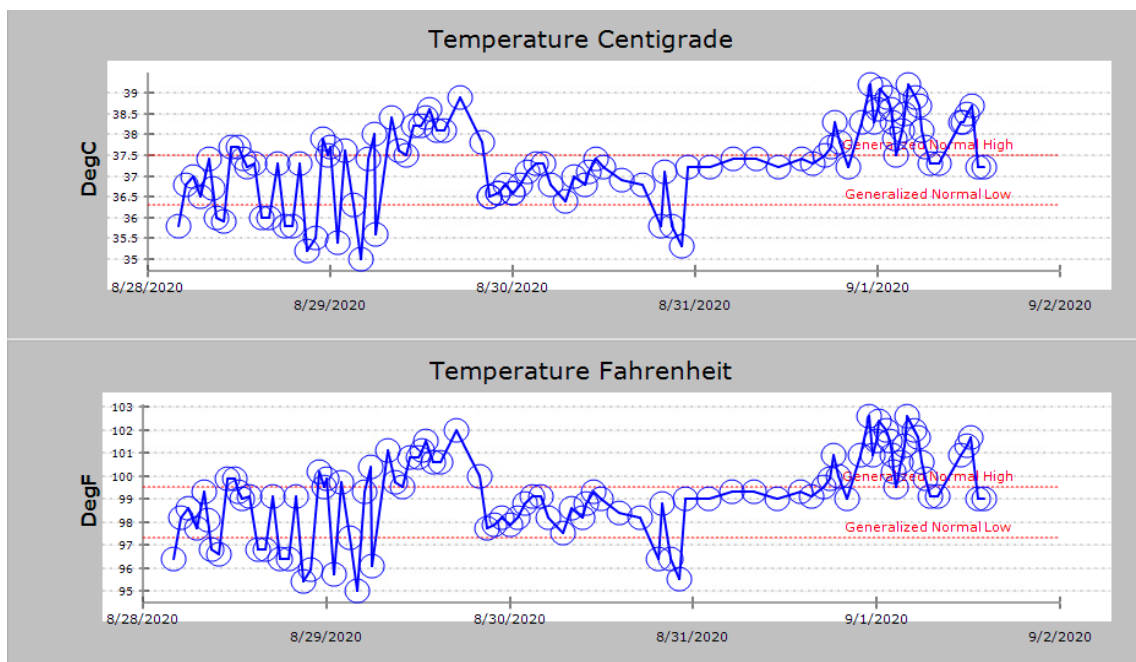


Figure 1. The newborn temperature instability between days of life 3 and 5.



Figure 2. Head Ultrasound showing grade III IVH

Studies in the adult population showed that the risk of central fever is higher in patients with ICH that are larger than those who had IVH and that the development of central fever had a negative impact on patient outcomes [6]. However, little data on central fever associated with ICH/IVH in the NICU population is available. Some of the few reported cases of central neonatal fever were discovered during the workup of fever with no other presenting symptoms for ICH/IVH, which was the case with our patient as well.

In a case report published in 2022, a term newborn presented with fever during the first newborn check was found to have IVH [8]. In a study that was conducted in Taiwan to estimate the incidences of ICH and fever in a hospital-based population and identify if there were differences in clinical features of neonatal ICH with and without hyperthermia, researchers found that the incidence of Intracranial hemorrhage to be higher in febrile neonates' group. They also noticed that some of these cases had neutrophil predominance in CSF, which could cause misdiagnosis as meningitis. In addition to the fact that intracranial hemorrhage with central fever might have subtle other presenting symptoms that make it go unrecognized, the researchers recommend cranial imaging to evaluate neonatal fever [9].

When considering noninfectious causes of temperature instability, we need to keep in mind that central causes can

present as hypo or hyperthermia. In a case report of a term baby with choroid plexus carcinoma, the authors report that the infant presented initially with hypothermia [10].

CONCLUSION AND RECOMMENDATIONS FOR CLINICIANS

There is a wide range of etiologies for neonatal fever. Although infectious etiologies need to be rolled out when assessing a NICU infant presenting with temperature instability, we need to keep our minds open to other etiologies, including causes of central fever.

Our patient's sudden drop in hematocrit was the abnormality that flagged ICH/IVH as the etiology of his temperature instability. CBC could be the key to many diagnoses and must be interpreted well.

Routine cranial ultrasound is usually done for infants less than 32 weeks of gestation; However, we need to keep a low threshold for considering cranial imaging in neonates born after 31 weeks of gestation who have evidence of noninfectious fever.

Further elaboration on central fever to help improve screening guidelines to avoid missing more cases of central fever and intracranial/intraventricular hemorrhage.

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