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Journal of Pediatric Endocrinology and Diabetes

Case Report

Hypopituitarism in a preterm infant with history of congenital syphilis and intraventricular hemorrhage

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Received : 18 October 2022
Accepted : 30 January 2023
Published : 11 April 2023

DOI
10.25259/JPED_34_2022

Quick Response Code:

ABSTRACT

A baby girl was born at 29 weeks and 2 days gestation with a physical examination notable for petechial rash, hepatosplenomegaly, and hydrops. The baby was born before the mother could be rescreened for syphilis and non-treponemal tests were positive at birth. The first weeks of life were complicated by clinical instability and post-hemorrhagic hydrocephalus that probably resulted from a combination of prematurity and syphilis. During the 2nd month of life, she showed a failure to thrive, persistent hypoglycemia, and diabetes insipidus and was diagnosed with hypopituitarism. Hormonal substitution treatment was challenging and required multiple adjustments until satisfactory control was attained.

Keywords: Congenital syphilis, Hypopituitarism, Neonatal intensive care, Pregnancy-related infectious complications, Hormone replacement therapy

INTRODUCTION

Hypopituitarism is defined as the deficiency of one or more pituitary hormones. Neonatal hypopituitarism may be congenital or acquired. Congenital causes include genetic mutations, developmental defects of the pituitary gland, and congenital infections. Birth asphyxia, trauma, and neonatal sepsis are some of the acquired perinatal causes. Diagnosis is challenging since findings may not be present in the neonatal period and the clinical picture is frequently non-specific.[1-3]

Congenital syphilis (CS) is an infectious disease caused by *Treponema pallidum* acquired through the placenta. Vertical transmission increases as the pregnancy advances but can occur at any time in gestation.[4] Untreated syphilis can severely compromise pregnancy outcomes and induce fetal and neonatal morbidity and mortality. Symptomatic central nervous system (CNS) involvement is rare, but hypopituitarism has been previously described.[4-6] Hypothalamic-pituitary axis dysfunction has been reported in children with intraventricular hemorrhage (IVH) and/or hydrocephalus.[1,2,7-10]

CASE REPORT

A girl was delivered at 29 weeks and 2 days gestation by urgent caesarean section with a birth weight of 1260 g. Her mother was a healthy 20-year-old woman who had received adequate prenatal care, including a negative screening for syphilis on the first trimester. Ultrasound

(US) evaluations at first and second trimesters showed no abnormalities; however, just before delivery it demonstrated hydrops fetalis. Maternal serological tests at the time of birth showed a rapid plasma reagin (RPR) titer of 1/64 and a positive *T. pallidum* hemagglutination test (TPHA); the remaining laboratory evaluation was normal.

At birth, the infant was bradycardic and showed no spontaneous breathing effort, requiring intubation, and resuscitation maneuvers; Apgar score was 4 at 1 min and 6 at 5 min. Physical examination showed generalized petechial and purpuric rash, hepatosplenomegaly, and hydrops. The infant had a RPR titer of 1/128 and a positive TPHA, suggesting CS and was treated with intravenous aqueous crystalline penicillin G, 50,000 units/kg for 10 days. Clinical course during the first week was further complicated by coagulopathy, liver dysfunction with cholestasis, and hemodynamic and respiratory instability. Skeleton radiographs performed during the first week showed signs of metaphysitis on the proximal ulnas.

Brain US on the first day of life (DOL) showed bilateral grade 2 IVH. Subsequent US revealed worsening IVH, with bilateral grade 3 IVH [Figure 1] that progressed to post-hemorrhagic hydrocephalus [Figure 2]. The patient was submitted to four ventricular punctures as an initial treatment option. After the 4th week of life, ventricular size and head circumference stabilized without any further intervention. Further on, head growth markedly decelerated, with a head circumference on the 26th percentile at DOL 34 and below the 3rd percentile at DOL 54. She also showed a failure to thrive: birth weight on the 60th percentile evolved to below the 3rd percentile at DOL 54 despite appropriate enteral feeding and caloric intake. Routine laboratory evaluation at 1 month was normal.

At 2 months, the patient presented recurrent asymptomatic prefeed hypoglycemia, followed by polyuria (>8 mL/kg/h). An elevated serum sodium (155 mmol/L), high serum osmolality (355 mOsm/kg), and low urine osmolality (148 mOsm/kg) suggested the diagnosis of diabetes insipidus (DI). Further, the investigation revealed a low cortisol level (2.8 μg/dL; normal: > 6.6 μg/dL), low growth hormone (GH) level (6.1 μg/L; normal: 7.6–47.1 μg/L), and low insulin-like growth factor-1 (<15.0 μg/L; normal: 18–172 μg/L). Given these multiple endocrine abnormalities, the diagnosis of hypopituitarism was entertained. The remaining hypothalamus-pituitary hormones and thyroid hormone levels were normal. In collaboration with the pediatric endocrinology team, it was decided to start a therapeutic trial of 1 μg/kg oral desmopressin. There was an initial drop in urinary output and serum osmolality; however, persistent hypernatremia prompted increased dosing. Variations in urine output required multiple therapeutic adjustments; hence, administration intervals and dosing were quite irregular during the first 2 weeks of treatment. Satisfactory clinical and biochemical control was later achieved with 3 μg/kg/dose every 12 h. Substitution treatment with oral hydrocortisone was initiated with 10 mg/m^2 body surface/day every 8 h.

Brain magnetic resonance imaging (MRI) at 40 weeks postmenstrual age showed cystic periventricular leukomalacia and cerebellar atrophy but a structurally normal pituitary gland [Figure 3]. Auditory and visual evoked potentials revealed bilateral neurosensory deafness and significant visual impairment. At that time, fundoscopy showed pale optic disks.

DISCUSSION

Symptoms of neonatal hypopituitarism depend on hormonal deficiencies and their severity and may include hypoglycemia, cholestasis, electrolyte abnormalities, hemodynamic instability, seizures, failure to thrive, and recurrent sepsis.[1-3]

We present the case of a preterm infant born with signs of CS who needed intensive care for 3 weeks. Treatment with penicillin was instituted at birth. Severe IVH progressing to post-hemorrhagic hydrocephalus required ventricular punctures until the 3rd week of life when hydrocephalus

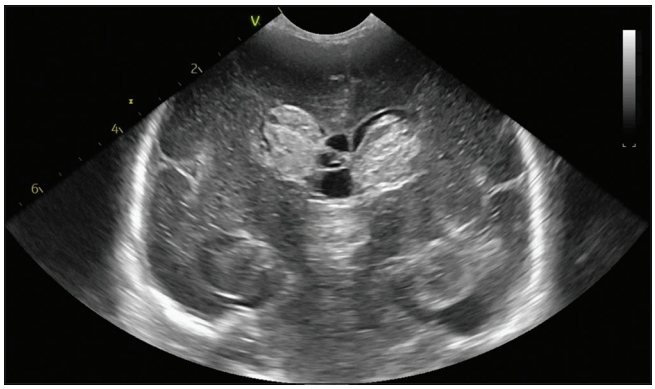

Figure 1: Brain US on DOL 7 showing bilateral grade 3 IVH. US: Ultrasound, DOL: Day of life, IVH: Intraventricular hemorrhage.

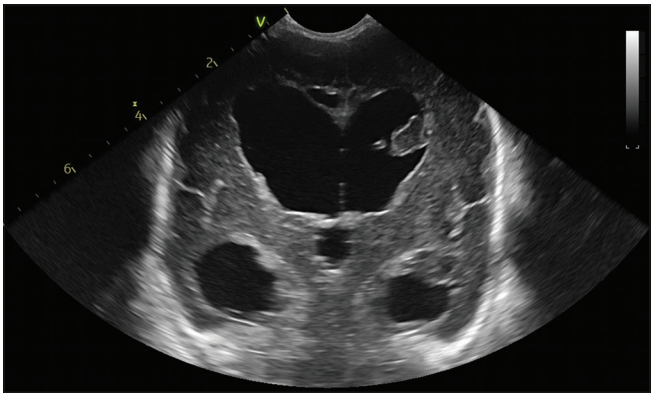

Figure 2: Brain US on DOL 14 showing post-hemorrhagic hydrocephalus. US: Ultrasound, DOL: Day of life.

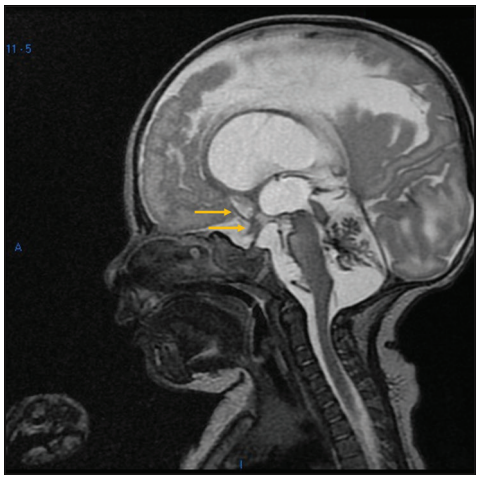

Figure 3: Brain MRI on DOL 78 showing a normal pituitary gland (yellow arrows), ventriculomegaly, cystic degeneration, and cerebellar atrophy. MRI: Magnetic resonance imaging, DOL: Day of life.

spontaneously improved. Subsequently, she developed asymptomatic hypoglycemia and polyuria.

Congenital hypopituitarism has been previously described as part of CNS involvement of CS. Two preterm infants with symptomatic CS at birth and later diagnosed with hypopituitarism had free thyroxine, cortisol, and GH deficiencies; the autopsy of one patient showed fibrosis of the anterior pituitary lobe with intact posterior lobe.[5] A full-term male born with non-specific symptoms of CS but only diagnosed at 3 months of age presented with hypothyroidism, DI, hypocortisolism, and hypoprolactinemia.[6] His MRI showed a normal anterior pituitary gland and pituitary stalk, although the posterior lobe could not be identified. Our patient's MRI also showed a structurally normal pituitary gland despite the clinical picture of hypopituitarism. Interstitial inflammation and fibrosis of the anterior pituitary lobe were commonly found in autopsies in the pre-penicillin era, and it has been suggested that many patients may have died from unrecognized and untreated hypopituitarism.[5,6] Most organ involvement results from hematogenous spread of treponema and local destruction mediated by the immune system, however pituitary lesions may also be secondary to infection and inflammation of surrounding tissues.[5,6]

Hydrocephalus has also been associated with hypothalamic-pituitary axis dysfunction. Blood flow variations and increased pressure are possible mechanisms of injury.[3,7] Two cases of central DI in preterm infants with post-hemorrhagic hydrocephalus have been reported, but both resolved with the hydrocephalus treatment.[9] DI has also been reported in preterm neonates with IVH without hydrocephalus;[7,8] however, to the best of our knowledge, there are no published cases of multiple hormone deficiencies.

Management of central DI in infants is challenging since their diet is fluid dependent, and they are unable to autonomously access adequate amounts of free water to prevent dehydration and hypernatremia. Fluid restriction is not appropriate in these young patients, because it would hinder adequate caloric needs. Desmopressin is an option for treatment, with urine output starting to decrease 1–2 h after administration and lasting for 6–18 h;[1,8] however, dosing is a matter of cautious experimentation. Overtreatment with desmopressin is more dangerous than undertreatment in this vulnerable cohort of patients and it is recommended to start with low doses since subsequent hyponatremia may be severe and associated with brain damage.[2] Intranasal desmopressin is 10–20 times more potent than oral desmopressin and nasal absorption might be irregular in newborns.[8] Preterm and term infants may evolve with anuria and marked drops in sodium levels a few hours after the first administration.[7,8] It is mandatory to monitor serum and urine osmolality, electrolytes, and weight during therapy. Recommendations about starting treatment are variable, from 0.5–1 μg/kg/dose to 2.5 μg/kg/dose of oral desmopressin, or 0.05–0.1 μg/kg/dose of intranasal desmopressin.[1,8] As our case illustrated, multiple dosing and interval adjustments are often required to achieve clinical and biochemical control. Recently, the use of a thiazide diuretic in association with low-solute formula has been proposed as a bridging treatment with lower risk.[2] More studies are needed in young and preterm infants, but it may be the favored alternative in the near future.

Hydrocortisone is the preferred treatment for cortisol deficiency given its milder impact on bone health compared to other glucocorticoids.[8] Since newborns have greater cortisol secretion rates than older children, higher doses of hydrocortisone are necessary and may later require to be titrated. One review suggests a total dose of 12–18 mg/m^2/day in three divided doses and another recommends starting with 9–12 mg/m^2/day in three to four divided doses.[1,2] Cortisol is important in water excretion so DI may develop after treatment is started. We opted to start low with 10 mg/m^2/day in three divided doses and reached adequate glycemic control at 14 mg/m^2/day. In periods of illness or stress, hydrocortisone dose should be doubled or tripled. Caregivers must be informed about emergency dosing and have a sick day plan. Because mineralocorticoid secretion is normal in central adrenal insufficiency, mineralocorticoid treatment is not necessary. Given the controversies in the diagnosis of GH deficiency in infants,[1,2] and since our patient achieved euglycemia with hydrocortisone dosing adjustment, it was decided to postpone GH therapy.

There are no published data on the prognosis of hypopituitarism associated with CS. In other forms of congenital hypopituitarism, follow-up is deemed essential since it is a lifelong condition, and some hormone deficiencies may appear later in the course of the illness.[1,2]

CONCLUSION

Congenital hypopituitarism encompasses a challenge in diagnosis and treatment. Any delay in replacement therapy may have severe consequences, given the vital importance of the pituitary gland. Our case reinforces that CS is a multiorgan disease that may present with rare clinical features; therefore, clinicians must be vigilant.

Acknowledgments

The authors would like to thank Dr. António Gomes for proofreading the article.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Castelbranco-Silva A, Martins M, da Cunha J. Hypopituitarism in a preterm infant with history of congenital syphilis and intraventricular hemorrhage. J Pediatr Endocrinol Diabetes 2022;2:131-4.