Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/19536
DOI URL: http://dx.doi.org/10.21474/IJAR01/19536

RESEARCH ARTICLE

PITUITARY STALK INTERRUPTION SYNDROME REVEALED BY SEVERE AND PERSISTENT NEONATAL HYPOGLYCEMIA

S. Rahmouni[1], K. Skalli[2], I. Jerrar Oulidi[3], El. Ouanouche[5,6], S. Stati[4], D. Oukachou[2] and F. Hmami[1,2]
[1]Faculty of Medicine and Pharmacy, Moulay Abdellah University, Fez, Morocco.
[2]Department of Neonatology and Neonatal Resuscitation Unit, University Hospital Hassan II, Fes, Morocco.
[3]Department of Internal Medicine,MUSC Health.
[4]Psychiatric Emergency Department, Arrazi Psychiatric University Hospital, Salé-Morocco.
[5]Higher Institute of Nursing and Health Technology of Tanger- Morocco.
[6]Biology and Health Department. Faculty of Science. Ibn Tofail University Kenitra-Morocco.

Manuscript Info

Manuscript History
Received: 28 July 2024
Final Accepted: 30 August 2024
Published: September 2024

Key words:-
Pituitary Stalk Interruption Syndrome, NeonatalHypoglycemia, Magnetic Resonance Imaging (MRI), Hormonal Replacement Therapy

Abstract

We present the case of a newborn who exhibited severe and persistent neonatal hypoglycemia without any apparent risk factors. The persistence of profound hypoglycemia, measured at 0.22 mmol/L, prompted an extensive biological workup that revealed a significant decrease of several pituitary hormones. The diagnosis of pituitary stalk interruption syndrome (PSIS) was confirmed by magnetic resonance imaging (MRI), which showed a complete interruption of the pituitary stalk. Prompt initiation of replacement therapy led to a notable clinical improvement and stabilization of blood glucose levels, thereby minimizing the risk of further hypoglycemic episodes.This case underscores the importance of broadening the etiological investigation in cases of persistent hypoglycemia without an obvious context, as hypoglycemia can be the sole clinical manifestation of PSIS. This congenital developmental anomaly of the pituitary gland represents a diagnostic emergency, and the prognosis is highly dependent on the prompt implementation of hormonal replacement therapy.

Introduction:-

Neonatal hypoglycemia affects 5 to 15% of all newborns[1]. At birth, the newborn must establish mechanisms to regulate blood glucose levels based on feeding status, unlike in utero, where there was a continuous placental transfer of glucose. This transition is made possible by an inversion of the glucagon/insulin ratio, allowing the newborn to mobilize hepatic (glycogen) and fat reserves[2].

Indeed, several metabolic and hormonal mechanisms come into play to balance glucose supply and demand. However, there are many risk situations where this delicate balance can be disrupted. When there is a mismatch between glucose production capacity and metabolic needs, there is a risk of hypoglycemia.

In the vast majority of cases, neonatal hypoglycemia is transient and occurs within the first 48 hours of life, usually in a suggestive context (prematurity, macrosomia, gestational diabetes, infection, growth restriction, anoxic-

Corresponding Author:-S. Rahmouni
ADDRESS:-Faculty of Medicine and Pharmacy, Moulay Abdellah University, Fez, Morocco.

ischemic events). However, when hypoglycemia persists beyond the third day of life, it is termed persistent. In this case, it is appropriate to investigate endocrine, metabolic, or hepatic causes.[3]

Endocrine-related hypoglycemia may be due to hyperinsulinism, congenital hypopituitarism, or peripheral or central cortisol insufficiency.[4]

We report the case of a newborn in whom neonatal hypoglycemia was the first indication of pituitary stalk interruption syndrome (PSIS). Pituitary stalk interruption syndrome is a very rare condition with an estimated incidence of 1 in 200,000 births[5]. This congenital developmental anomaly of the pituitary gland is a diagnostic emergency, with the prognosis depending on the speed of hormone replacement therapy initiation. Hormonal deficiency in newborns with pituitary stalk interruption syndrome is usually multiple, with somatotrope deficiency found in all patients, necessitating the exploration of various anterior pituitary axes.

Observation:-

We report the case of a male newborn from a non-consanguineous marriage, with a normally conducted pregnancy, born at term via cesarean section due to breech presentation. There was no notable family history, including maternal diabetes. At birth, the newborn showed good adaptation to extrauterine life, with a birth weight of 3700g.

However, a few hours after birth, the newborn exhibited lethargy with significant hypotonia. Capillary blood glucose levels revealed profound hypoglycemia below 0.22 mmol/L (normal > 2.6 mmol/L), initially requiring oral, then intravenous glucose supplementation, followed by glucagon administration. Due to persistent hypoglycemia, the newborn was transferred to the university hospital on the 4th day of life for further investigation.

Clinical examination upon admission revealed slight hypotonia with difficulty in sucking, and cutaneous-mucosal jaundice. The abdomen was soft, with no hepatomegaly, while the genital examination revealed bilateral cryptorchidism. The remainder of the examination was normal, notably with no dysmorphism or hemihypertrophy.

The complete blood count showed white blood cells: 4470/mm³, neutrophils: 1460/mm³, hemoglobin: 16.4 g/L, platelets: 37,000/mm³, and C-reactive protein (CRP) was elevated at 33 mg/L. The blood ionogram confirmed hypoglycemia, and total serum bilirubin was 178 mg/L with direct bilirubin at 39 mg/L. Transaminases were normal. The newborn received intensive phototherapy and a 10-day course of antibiotic therapy until CRP levels normalized, alongside intravenous glucose infusion of 10%.

Due to persistent neonatal hypoglycemia, an expanded etiological assessment was conducted. The urine strip test revealed the presence of acetone, and the glucagon test did not show a significant increase in blood glucose. Similarly, insulin levels during hypoglycemia were 1.66 mUI/L (>2 mUI in cases of hyperinsulinemia), ruling out neonatal hyperinsulinemia.

Hormonal assessment showed involvement of various pituitary axes. The corticotropic function was impaired, with cortisol levels collapsing to 52 nmol/L (<150 nmol/L) during hypoglycemia, associated with a significant drop in adrenocorticotropic hormone (ACTH) to 18.7 ng/L (50-60 ng/L). Thyroid function tests revealed central hypothyroidism with free thyroxine (T4L) decreased to 0.77 ng/dL (1.3-2.8 ng/dL), free T3 at 1.67 pg/mL (2-5.2 ng/dL), without an increase in thyroid-stimulating hormone (TSH). The somatotropic and gonadotropic axes showed a collapse in growth hormone (GH): 1 ng/mL (<6 ng/mL) and insulin-like growth factor 1 (IGF1): 11.10 ng/mL, as well as follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels (respectively 0.90 mUI/mL (1-2 mUI/mL) and 3.14 mUI/mL [0.5-6.5 UI/L]).

The hormonal deficits across different pituitary axes, along with clinical morphological anomalies, indicated congenital pituitary deficiency. To determine the etiology of the pituitary insufficiency, the child underwent contrast-enhanced MRI of the brain, which revealed significant hypoplasia of the anterior pituitary, complete interruption of the pituitary stalk, and ectopic posterior pituitary, leading to the diagnosis of pituitary stalk interruption syndrome (PSIS).

Emergency treatment with hydrocortisone was initiated, leading to a dramatic improvement in tone and preventing further hypoglycemic episodes. Subsequent L-thyroxine substitution resulted in good clinical progress for the infant.

The newborn was then transferred to a pediatric endocrinology unit, where close clinical and biological monitoring was established to track growth and evaluate the effectiveness of the therapeutic protocol.

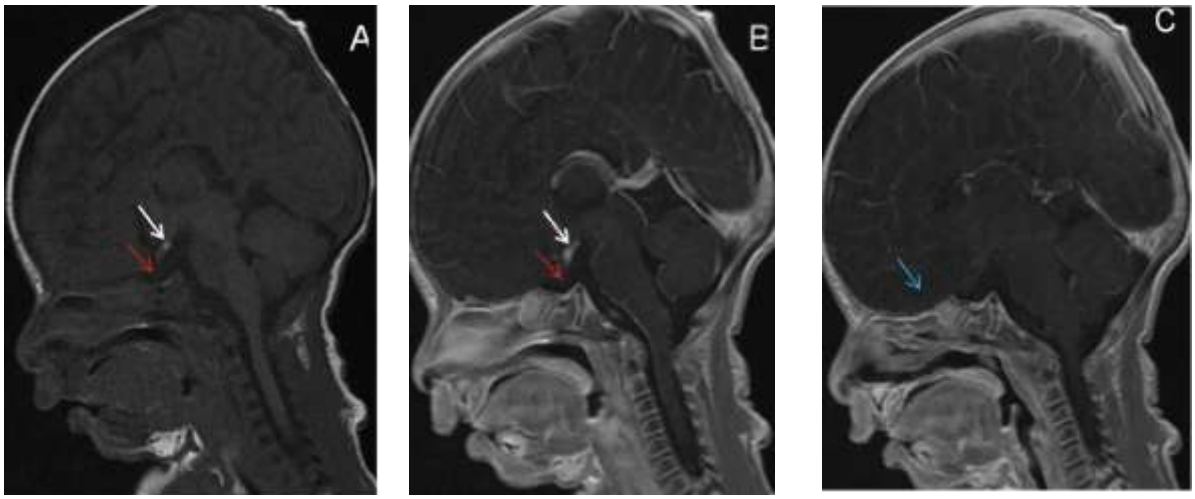

Figure 1:-MRISequences: A: Sagittal T1 / B-C: Sagittal T1 C+

MRI images show an ectopic posterior pituitary at the level of the median eminence with spontaneous hyperintensity on T1 (white arrow), a very thin appearance of the pituitary stalk (red arrow), and an underdeveloped anterior pituitary relative to age.

Discussion:-

Neonatal hypoglycemia is common in the presence of risk factors such as prematurity, macrosomia, gestational or insulin-dependent diabetes, maternal beta-blocker treatment, infection, and hypotrophy[1]. Neonatal hypoglycemia is defined as a blood glucose level below 2.6 mmol/L or 0.47 g/L according to the literature[6].

In the vast majority of neonatal hypoglycemia cases, the context is suggestive, and hypoglycemia is detected before symptoms appear in at-risk newborns during the first 48 hours of life. After implementing the previously mentioned measures, glucose homeostasis is well regulated within a few days, and there is no indication to conduct an etiological workup. However, if hypoglycemia persists beyond the third day of life, appears in newborns without risk factors (often symptomatic), and/or requires high glucose intake (greater than 15 g/kg/day), it becomes necessary to search for an endocrine, metabolic, or hepatic cause[3].

Endocrine causes are rare, thus poorly understood and rarely explored[4]. Persistent neonatal hypoglycemia can be the only clinical manifestation of congenital pituitary deficiency[7]. In our case, the persistence of hypoglycemia without a suggestive context alerted the medical team. The team meticulously documented the characteristics of hypoglycemic episodes: frequency, severity of hypoglycemia, and response to treatment. A thorough clinical examination was then conducted to identify other clinical signs that could guide the diagnosis, such as dysmorphia, hypotonia, jaundice, asthenia, micropenis, cryptorchidism, or hepatomegaly.

Biological investigations to determine the etiology of neonatal hypoglycemia included searching for an infectious cause (maternal-fetal infection), an anomaly in intermediary energy metabolism, and endocrine disturbances. Initially, hormone levels involved in glucose metabolism regulation were measured (cortisol, GH, insulin, and C-peptide), supplemented by hormonal studies of various pituitary axes (FSH, LH, TSH, T4L, T3L, prolactin). The results revealed a multiple hormone deficiency of the pituitary gland. Brain MRI revealed a complete interruption of the pituitary stalk, indicating pituitary stalk interruption syndrome (PSIS).

Pituitary stalk interruption syndrome (PSIS) was first described by Fujisawa in 1987[8].. It is a very rare condition with an estimated incidence of 1 in 200,000 births [5]. This syndrome is particularly common in male newborns and those born in a breech position [9]. It is characterized by a structural anomaly of the hypothalamic-pituitary axis,

leading to multiple hormonal deficiencies. The syndrome is defined by morphological anomalies seen on MRI: an invisible pituitary stalk, hypoplasia of the pituitary gland, and an ectopic posterior pituitary[8].

Several etiopathogenic hypotheses have been proposed for PSIS. The first was the hypothesis of brain trauma during childbirth. However, this hypothesis is now considered outdated, as most patients do not exhibit trauma during pregnancy or delivery[10].Moreover, the presence of malformative syndromes (such as anal imperforation, ophthalmological or central nervous system involvement) or familial cases suggests a prenatal and likely genetic origin of the disease[11]. A hypothesis of abnormal fetal pituitary development has been proposed, with mutations identified in a limited number of cases in the HESX1, LHX4, OTX2, and SOX3 genes, which encode transcription factors involved in organogenesis, particularly in the development of the hypothalamus and pituitary structures (sella turcica, pituitary stalk) [12]. However, these mutations account for only 5% of PSIS cases, suggesting the involvement of other genes yet to be discovered.

PSIS is typically diagnosed during the neonatal period. Clinical signs may vary but often include early and recurrent hypoglycemia, systemic hypotension, and prolonged jaundice. These symptoms may be associated with manifestations of congenital hypothyroidism, such as macroglossia, large fontanelles, and hypothermia. External genital abnormalities, such as micropenis and/or cryptorchidism, are also common. Notably, the frequency of hypoglycemia and the prevalence of micropenis are significantly higher in patients with PSIS compared to other causes of pituitary insufficiency[13]. In our case, only cryptorchidism was present, without micropenis.

A later diagnosis of PSIS could be explained by a less severe endocrine involvement. In such cases, PSIS is generally diagnosed during the investigation of growth retardation. Mild, spontaneously resolving hypoglycemia during the neonatal period may have been present but undetected[14]. Due to the frequency of hypoglycemia in at-risk newborns, therapeutic management is often prioritized over etiological investigation. However, etiological assessment, which is easy to perform and does not delay therapeutic management, allows for appropriate treatment [6].This assessment should be systematic in the absence of risk factors or if hypoglycemia persists beyond the expected duration. A strong suspicion of congenital hypopituitarism warrants a biological etiological workup[3].

In the first weeks of life, the kinetics of hormone secretion are unique (absence of circadian rhythm, adaptive processes), making it difficult to interpret biological assays. Brain MRI is a key examination in diagnosing pituitary development anomalies. Therefore, the diagnosis of hypopituitarism is based on a combination of clinical, biological, radiological, and possibly genetic evidence. Biological exploration of the anterior pituitary axes involves measuring various pituitary hormones or their targets: GH or IGF1; TSH or T4L and T3L; ACTH or cortisol; DHEA-S, FSH, LH, or testosterone.

For somatotropic deficiency: Stimulation tests are inappropriate or contraindicated before the age of 6 months[15]. The diagnosis will be based on a combination of findings: recurrent hypoglycemia (its absence does not rule out the diagnosis), the presence of other deficiencies, reduced insulin-like growth factor (IGF)-I and insulin-like growth factor-binding protein (IGFBP3) levels (normal values do not rule out the diagnosis), and a basal GH measurement of less than 5 ng/ml within the first 7 days of life. During spontaneous hypoglycemia, the absence of a GH elevation is highly non-specific and is not a reliable diagnostic criterion[16].

Thyrotropic deficiency is confirmed by a decrease in free thyroid hormones (T4 and T3) without a significant increase in TSH (according to age-specific and assay-specific references) [17].

For corticotropic deficiency, the absence of a circadian rhythm during the first months makes diagnosis difficult, possibly leading to overdiagnosis. A low cortisol level during spontaneous hypoglycemia is highly non-specific and is not a reliable diagnostic criterion. The diagnosis will be based on repeated cortisol and ACTH measurements at different times or a synacthen test[18].

Gonadotropic deficiency can be confirmed during the minipuberty period (15 days to 3 months of life in boys, slightly longer in girls, without clinical manifestations). In boys, the diagnosis can be suspected with a testosterone level below 1 ng/ml and an anti-Müllerian hormone (AMH) level below 200 pmol/l during the first 3 days of life (LH and FSH are not contributory at this stage), and confirmed by the absence of elevation of LH and FSH, testosterone, AMH, inhibin B during minipuberty (approximately 10 days to 3 months). In girls, the diagnosis is based on decreased LH and FSH levels during minipuberty (the first 3 years of life) [19].

Treatment must be initiated urgently to correct hypoglycemia and prevent recurrence. It involves substituting the various anterior pituitary deficiencies. The recommended hydrocortisone replacement dose is 15 mg/m²/day, divided into 2 or 3 daily oral doses, with increased doses during infectious or stressful episodes. Central hypothyroidism replacement therapy involves oral levothyroxine, with an initial dose of 8-10 µg/kg/day (solution) for profound hypothyroidism (T4L < 5 pmol/L), or more commonly 5-7 µg/kg/day if hypothyroidism is less severe, administered once daily. The recommended GH replacement dose is 25 to 35 µg/kg/day, administered subcutaneously in the evening and adjusted based on clinical response and IGF-I levels[20].

The prognosis for PSIS is relatively good, provided that treatment begins at birth and hormones (cortisol, L-thyroxine, GH) are quickly replaced, and that the family receives adequate education. Follow-up should be regular in pediatric endocrinology consultations, initially monthly in infants, then quarterly to semi-annually in children and adolescents

Conclusion:-

Our observation emphasizes the importance of a systematic and rigorous etiological diagnostic approach in cases of persistent neonatal hypoglycemia without identified risk factors. It is essential to investigate the cause according to the three nosological groups (metabolic, endocrine, or hepatic), based on clinical examination and biological assessment findings. Persistent hypoglycemia can indeed be the only clinical manifestation of congenital hypopituitarism.

Pituitary stalk interruption syndrome (PSIS) is a rare condition, and its neonatal onset constitutes a diagnostic and therapeutic emergency. This pathology typically presents in the neonatal period with hypoglycemia. Early initiation of hormone replacement therapy significantly improves the prognosis, preventing long-term complications in growth and neurological development.

Given the complexity of interpreting hormonal assays at birth, close clinico-biological collaboration is crucial for the rapid diagnosis of PSIS and for tailoring short- and long-term therapeutic management.

References:-

[1] J. Stark, B. Simma, et A. Blassnig-Ezeh, « Incidence of hypoglycemia in newborn infants identified as at risk », The Journal of Maternal-Fetal & Neonatal Medicine, vol. 33, no 18, p. 3091-3096, sept. 2020, doi: 10.1080/14767058.2019.1568985.

[2] « Des lignes directrices pour le dépistage des nouveau-nés vulnérables à l'hypoglycémie - PMC ». Consulté le: 30 juillet 2024. [En ligne]. Disponible sur: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2724152/

[3] « Hypoglycémie néonatale - Pédiatrie », Édition professionnelle du Manuel MSD. Consulté le: 30 juillet 2024. [En ligne]. Disponible sur: https://www.msdmanuals.com/fr/professional/pédiatrie/troubles-métaboliques,-électrolytiques-et-toxiques-chez-le-nouveau-né/hypoglycémie-néonatale

[4] O. Delmas et al., « Hypoglycémie néonatale sévère et récidivante sans perte de sel révélatrice d'un syndrome de résistance à l'ACTH », Archives de Pédiatrie, vol. 21, no 12, p. 1353-1358, déc. 2014, doi: 10.1016/j.arcped.2014.09.010.

[5] S. El Chehadeh-Djebbar et al., « 17q21.31 microdeletion in a patient with pituitary stalk interruption syndrome », Eur J Med Genet, vol. 54, no 3, p. 369-373, 2011, doi: 10.1016/j.ejmg.2011.03.001.

[6] E. W. Y. Tam et al., « Hypoglycemia is associated with increased risk for brain injury and adverse neurodevelopmental outcome in neonates at risk for encephalopathy », J Pediatr, vol. 161, no 1, p. 88-93, juill. 2012, doi: 10.1016/j.jpeds.2011.12.047.

[7] S. Mehta et P. C. Brar, « Severe, persistent neonatal hypoglycemia as a presenting feature in patients with congenital hypopituitarism: a review of our case series », Journal of Pediatric Endocrinology and Metabolism, vol. 32, no 7, p. 767-774, juill. 2019, doi: 10.1515/jpem-2019-0075.

[8] I. Fujisawa et al., « Transection of the pituitary stalk: development of an ectopic posterior lobe assessed with MR imaging », Radiology, vol. 165, no 2, p. 487-489, nov. 1987, doi: 10.1148/radiology.165.2.3659371.

[9] D. Ibrahim, « Pituitary stalk interruption syndrome | Radiology Reference Article | Radiopaedia.org », Radiopaedia. Consulté le: 31 juillet 2024. [En ligne]. Disponible sur: https://radiopaedia.org/articles/pituitary-stalk-interruption-syndrome-1?lang=us

[10] T. Boueilh et al., « Pituitary stalk interruption syndrome: a rare and severe cause of pituitary deficiency Laboratory diagnosis of a newborn case », Annales de biologieclinique, vol. 75, no 2, p. 215-221, mars 2017, doi: 10.1684/abc.2017.1222.
[11] A. G. Ioachimescu, A. H. Hamrahian, M. Stevens, et R. S. Zimmerman, « The pituitary stalk transection syndrome: multifaceted presentation in adulthood », Pituitary, vol. 15, no 3, p. 405-411, sept. 2012, doi: 10.1007/s11102-011-0337-9.
[12] R. Reynaud et al., « Pituitary stalk interruption syndrome in 83 patients: novel HESX1 mutation and severe hormonal prognosis in malformative forms », Eur J Endocrinol, vol. 164, no 4, p. 457-465, avr. 2011, doi: 10.1530/EJE-10-0892.
[13] E. Masson, « Prématurité : définitions, épidémiologie, étiopathogénie, organisation des soins », EM-Consulte. Consulté le: 22 juillet 2024. [En ligne]. Disponible sur: https://www.em-consulte.com/article/300871/prematurite-definitions-epidemiologie-etiopathogen
[14] C. Bar et al., « Pituitary Stalk Interruption Syndrome from Infancy to Adulthood: Clinical, Hormonal, and Radiological Assessment According to the Initial Presentation », PLoS One, vol. 10, no 11, p. e0142354, 2015, doi: 10.1371/journal.pone.0142354.
[15] G. Binder, M. Weidenkeller, G. Blumenstock, M. Langkamp, K. Weber, et A. R. Franz, « Rational approach to the diagnosis of severe growth hormone deficiency in the newborn », J Clin Endocrinol Metab, vol. 95, no 5, p. 2219-2226, mai 2010, doi: 10.1210/jc.2009-2692.
[16] K. Hussain, P. Hindmarsh, et A. Aynsley-Green, « Spontaneous hypoglycemia in childhood is accompanied by paradoxically low serum growth hormone and appropriate cortisol counterregulatory hormonal responses », J Clin Endocrinol Metab, vol. 88, no 8, p. 3715-3723, août 2003, doi: 10.1210/jc.2003-030137.
[17] L. Persani et al., « 2018 European Thyroid Association (ETA) Guidelines on the Diagnosis and Management of Central Hypothyroidism », oct. 2018, doi: 10.1159/000491388.
[18] Y. Reznik et al., « SFE/SFEDP adrenal insufficiency French consensus: Introduction and handbook », Ann Endocrinol (Paris), vol. 79, no 1, p. 1-22, févr. 2018, doi: 10.1016/j.ando.2017.12.001.
[19] U. Boehm et al., « Expert consensus document: European Consensus Statement on congenital hypogonadotropic hypogonadism--pathogenesis, diagnosis and treatment », Nat Rev Endocrinol, vol. 11, no 9, p. 547-564, sept. 2015, doi: 10.1038/nrendo.2015.112.
[20] S. Castets et al., « Diagnostic et prise en charge du déficit hypophysaire congénital en pédiatrie », Perfectionnement en Pédiatrie, vol. 5, no 4, p. 279-287, déc. 2022, doi: 10.1016/j.perped.2022.10.011.