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RESEARCH ARTICLE

HYPOGLYCEMIA AND CHOLESTASIS IN NEWBORNS: CONSIDER PITUITARY STALK INTERRUPTION SYNDROME

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Abstract

Pituitary stalk interruption syndrome (PSIS) is a rare condition. This congenital anomaly affecting the development of the pituitary gland constitutes a diagnostic emergency, with the prognosis depending on the rapid initiation of hormone replacement therapy. Clinical manifestations associated with endocrine hormone deficiency vary according to the age of onset. In older children and adults, most patients present with short stature or hypogonadism. Neonatal PSIS is extremely rare and difficult to diagnose due to the absence of dwarfism, but a late diagnosis could have detrimental short- and long-term consequences. Therefore, early identification of clinical features is of great importance. Here, we report a case of neonatal PSIS revealed by cholestatic jaundice with hypoglycemia, with the initial assessment suggesting central adrenal insufficiency leading to the performance of a hypothalamic-pituitary MRI objectifying a pituitary stalk interruption syndrome. Initial response was favorable after hormone replacement therapy.

Introduction:-

Pituitary stalk interruption syndrome (PSIS) is a congenital anomaly in the development of the pituitary gland. It comprises the triad ofthin or interrupted pituitary stalk, aplasia or hypoplasia of anterior pituitary gland, and absent or ectopic posterior pituitary gland. It is usually diagnosed in the context of anterior pituitary insufficiency with variable clinical presentations. There are multiple reports of late-onset PSIS, while neonatal PSIS remains rarely reported. The manifestations of neonatal PSIS are complex and severe, sometimes life-threatening. Persistent hypoglycemia and jaundice in newborns may be the only indicative signs at neonatal age. As a result, many cases undergo extensive diagnostic testing before suspecting an endocrine disorder, delaying treatment and exposing patients to serious complications.

Case Report:

We report the case of a male newborn admitted to the neonatology department 18 hours after birth forrespiratory distress and feeding difficulties. He was born from a normal pregnancy carried to 42 weeks of gestation, delivered via caesarean section due to macrosomia. Upon admission, the examination revealed a pink, tonic, and responsive newborn with a weak sucking reflex, blood glucose level at 0.62 g/dl,and a Silverman score of 2/10. Other vital parameters were normal. The baby was macrosomic, weighing 4,200 grams (+2 SD), with normal height and head

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circumference (49 cm and 35 cm, respectively). Examination of the external genitalia revealed a micropenis measuring 1.5 cm, with no other midline abnormalities. The initial assessment was in favor of an early maternal-fetal infection.

During hospitalization, the newborn presented with episodes of hypoglycemia and developed jaundice on day 3 of life, initially non cholestatic, then progressively cholestatic, withtotal and direct bilirubin (BT/BD) levels of 141/76 mg/l respectively and GGT level : 851 IU/L. 5days after admission, the newborn presented with convulsive seizures secondary tosevererefractoryhypoglycemiaat 0.2 g/dl . An etiological blood work wasperformed (Table 1), which revealed extremely low cortisol levelsat 0.2ug/dl (3.7-19.4 ug/dl) with normalACTH level of 5.5 ng/l (5-60 ng/l). Given the central adrenal insufficiency, a hypothalamic-pituitary MRI was performed,showing hypoplasia of the anterior pituitary lobe, absence of the pituitarystalk and an ectopic posterior pituitary lobe located at the floor portion of the 3rd ventricle (Figure1). Thus, the diagnosis of pituitary stalk interruption syndrome (PSIS) was confirmed.Treatment with Hydrocortisone® was promptly initiated, first intravenously and then orally, preventing further hypoglycemic episodes, with progressive regressionof cholestasis. A hypophyseogramwas conducted, initially showing intact thyrotropic and gonadotropic axes (Table 1). The child, lost to follow-up, returned at 18 months with adrenal crisis.Clinical examination revealed a statural delay with a height of 70cm (-3SD) and persistent micropenis.Further exploration of other axes showed central hypothyroidism, with low free thyroxine (FT4) at 7.25 pmol/L [9-19 pmol/L], with normal thyroid stimulating hormone (TSH) levels. The gonadotropic axis showed collapsed levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) (0.05 IU/L [0.2-3.5 IU/L] and less than 0.1 IU/L [0.5-6.5 IU/L], respectively). IGF1 was at the lower limit. The growth hormone (GH) test was interrupted due to severe hypoglycemia. The treatment consisted of hormone replacement with L-thyroxine (3.5 µg/kg/day) and adjustment of the hydrocortisone dosage. GH therapy has not yet been initiated.

Table 1:- Table showing the biological test results of our patient.

Parameter	**Values at Birth (Neonatal)**	**Normal Values at Birth**	**Values at 18 Months**	**Normal Values at 18 Months**
Glycemia (g/L)	0.2	0.40-0.60	0.4	0.70-1.00
Total Bilirubin (BT) (mg/L)	106	< 50	-	< 20
Direct Bilirubin (BD) (mg/L)	76	< 20	-	< 5
GGT (UI/L)	851	< 200	-	< 30
Cortisol (µg/dL)	0.2	3.7-19.4	3.5	3.7-19.4
ACTH (ng/L)	5.5	5-60	5.5	5-60
Free Thyroxine (T4L) (pmol/L)	9.8	9-19	7.25	9-19
Thyroid Stimulating Hormone (TSH) (mIU/L)	1.1	0.5-10	0.79	0.5-6
Follicle-Stimulating Hormone (FSH) (UI/L)	0.5	0.2-3.5	0.05	0-3
Luteinizing Hormone (LH) (UI/L)	0.7	0.5-6.5	< 0.1	1.7-8.6
IGF-1 (ng/mL)	-	Variable according to age	12.8	12.5-120

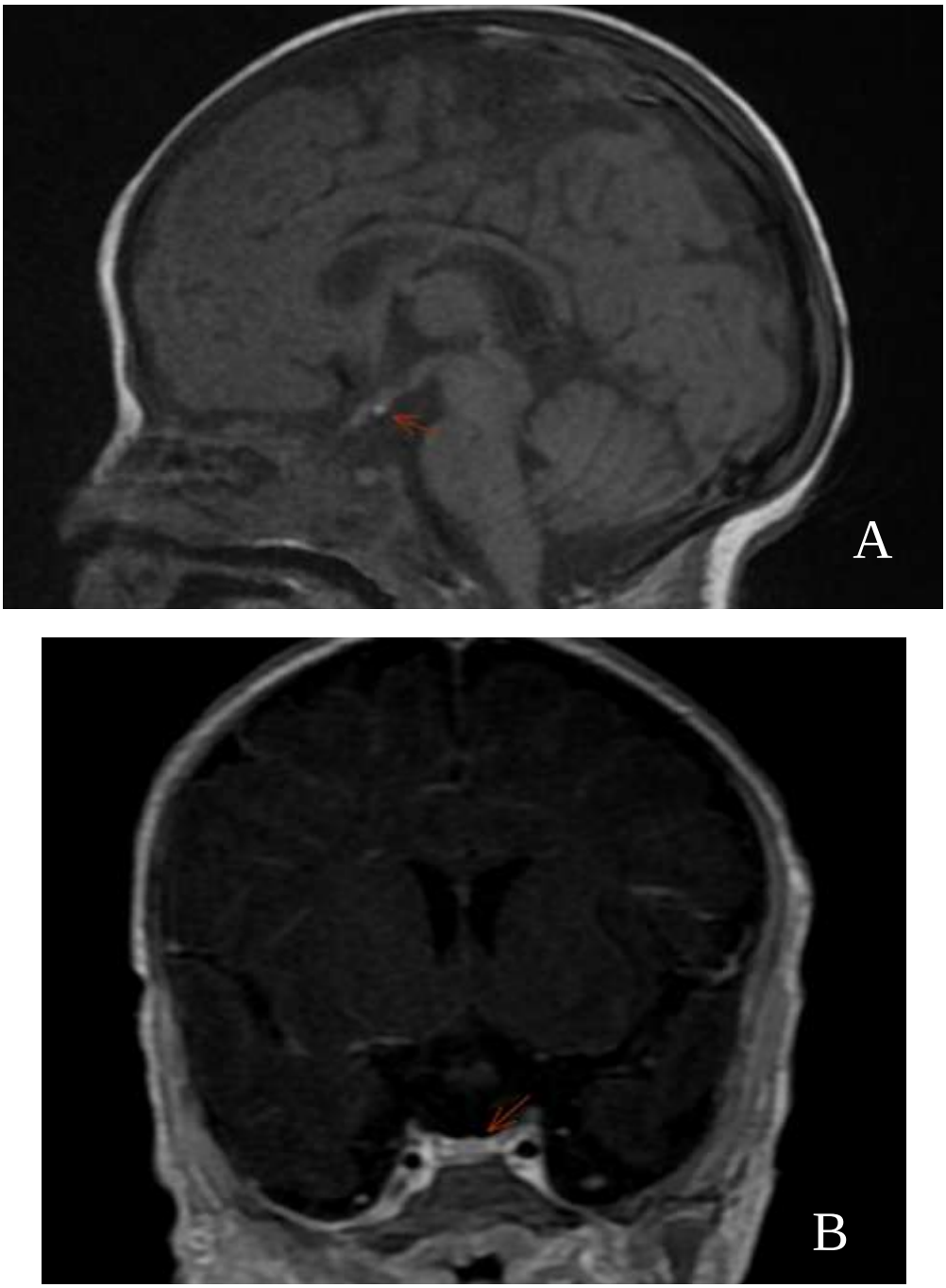

Figure 1:- A: Sagittal T1 MRI image depicting a physiologically hyperintense posterior pituitary gland in an ectopic position at the level of the third ventricle floor. **B:** Coronal T1-weighted section post gadolinium injection showing a normal morphology and enhancement of the anterior pituitary gland, with no individualization of the pituitary stalk.

Discussion:-

Pituitary stalk interruption syndrome (PSIS) was first described by Fujisawa in 1987[1]. It is anextremely rare condition, with an estimated incidence of 1/200,000 births. Around 1,000 cases have been reported in the literature, with a male predominance in 70% of cases, suggesting X-linked transmission. The cause of PSIS remains unknown, with several proposed theories including perinatal injuries or defective organogenesis due to genetic or environmental factors during pregnancy [2-3]. Rare mutations in HESX1, LH4, OTX3 and SOX3may cause PSIS in familial cases [4].

PSIS is a congenital pituitary anomaly, anatomically defined by a pathognomonic triad of three morphological abnormalities: hypoplastic anterior lobe, ectopic posterior lobe and thin or interrupted pituitary stalk [5]. This interruption can prevent the pituitary from receiving the necessary signals from the hypothalamus to produce and release hormones, leading to anterior pituitary hormone deficiency. Children with PSIS may present with either isolated growth hormone deficiency (GHD), or combined pituitary hormone deficiency (CPHD), affecting at least two anterior pituitary hormone axes. Earlier onset increases the likelihood of developing CPHD [4].Wang et al. found the prevalence of deficiency to be 100%, 97.2%, 88.2% and 70.3%, for GH, gonadotropins, corticotropin and thyrotropin, respectively [7].

A deficiency in one or more of these hormones can have potentially dramatic consequences. In our case, severe neonatal hypoglycemia alerted the medical team, highlighting the urgency of recognizing this condition due to its severe neurological consequences if unrecognized.

Clinically, PSIS can manifest in approximately 15% of patients during the neonatal period [8]. The clinical presentation varies and may include early and recurrent hypoglycemia, systemic hypotension; prolonged jaundice possibly associated with other signs of congenital hypothyroidism, and external genitalia abnormalities like micropenis and/or unilateral or bilateral cryptorchidism. The frequency of hypoglycemic episodes and the prevalence of micropenis are significantly higher in patients with PSIS compared to other causes of pituitary insufficiency [9]. Both signs were present in our patient, reinforcing the suspicion of this syndrome.

In our case, persistent hypoglycemia, jaundice and micropenis were revealing clinical signs. In PSIS, hypoglycemia results from deficiencies in glucose-inducing hormones such as GH, adrenal corticosteroid hormone, and thyroxine. Prolonged jaundice is probably due to reduced cortisol and hypothyroidism. Data analysis shows a strong correlation between cholestasis and low plasma cortisol levels. In nine children with cholestasis due to hypopituitarism, liver biopsies revealed decreased expression of canalicular transport proteins involved in biliary secretion (bile salt export pump, multidrug resistance protein 3 and multidrug resistance-associated protein 2). Glucocorticoids regulate gene transcription of these proteins through various receptors, either directly or via the C-terminal binding protein 3 transcription factor [10-11].

The somatotropic axis may not be completely affected in some cases of PSIS due to several reasons. Firstly, GH production may be less dependent on the hypothalamus compared to other hormones. In some cases, the pituitary can sustain a basal GH production even without hypothalamic stimulation via Growth Hormone-Releasing (Hormone Partial GH autonomy).Secondly, Compensatory mechanisms in the pituitary gland may allow a certain reserve of GH, sufficient to maintain certain metabolic functions despite disruption of the somatotropic axis [12].

Hypothalamic-pituitary MRI remains a key element for confirming the diagnosis, which will be first suggested by the clinical and biological profile. Biological investigation of anterior pituitary axes involves assessing various pituitary hormones or their targets: GH or IGF1; TSH or free T4 and T3, ACTH or cortisol, DHEA, FSH, LH or testosterone. It is therefore necessary to investigate other pituitary deficiencies in newborns with PSIS. Indeed, in PSIS, hormone production across various axes may not always be severely impaired, and the patient may present a variable phenotype. It should be noted that other hormonal deficiencies mightdevelop during follow-up [13].

After diagnosis, hormone replacement therapy should begin with cortisol followed by thyroxine, as restoring aneuthyroid state can destabilize a patient with ACTH deficiency [14]. Growth hormone therapy is often required later in childhood.

The prognosis of newborns with PSIS depends on the rapidity and effectiveness of hormonal management. With appropriate treatment, children can achieve relatively normal growth and development. However, long-term medical follow-up is required to adjust treatments and monitor disease progression.

Conclusion:-

Our case report highlights the importance of recognizing persistent hypoglycemia and jaundice innewborns as potential indicators of PSIS. Early diagnosis and initiation of hormonereplacement therapy is crucial to prevent potentially fatal complications and ensure betterlong-term outcomes.

References:-

1. Gutch M, Kumar S, Razi SM, Saran S, Gupta KK. Pituitary stalk interruption syndrome: Case report of three cases with review of literature. J PediatrNeurosci. 2014 May;9(2):188-91. doi: 10.4103/1817-1745.139363. PMID: 25250085; PMCID: PMC4166852.
2. Tauber M, Chevrel J, Diene G, Moulin P, Jouret B, Oliver I, Pienkowski C, Sevely A. Long-term evolution of endocrine disorders and effect of GH therapy in 35 patients with pituitary stalk interruption syndrome. Horm Res. 2005;64(6):266-73. doi: 10.1159/000089425. Epub 2005 Oct 15. PMID: 16260897.
3. Melo ME, Marui S, Carvalho LR, Arnhold IJ, Leite CC, Mendonça BB, Knoepfelmacher M. Hormonal, pituitary magnetic resonance, LHX4 and HESX1 evaluation in patients with hypopituitarism and ectopic posterior pituitary lobe. ClinEndocrinol (Oxf). 2007 Jan;66(1):95-102. doi: 10.1111/j.1365-2265.2006.02692.x. PMID: 17201807.
4. Pinto G, Netchine I, Sobrier ML, Brunelle F, Souberbielle JC, Brauner R. Pituitary stalk interruption syndrome: a clinical-biological-genetic assessment of its pathogenesis. J ClinEndocrinolMetab. 1997 Oct;82(10):3450-4. doi: 10.1210/jcem.82.10.4295. PMID: 9329385.
5. I.Guemmi, Rihab Aissaoui, Mohammed Leknani, Hajar Siouri, Narjisse Aichouni, Imane Kamaoui, Siham Nasr i, Imane Skiker Le syndrome d'interruption de la tige pituitaire : apport de l'imagerie Volume 50, Issue 2, March 2023.10.1016/j.neurad.2023.01.105
6. Boueilh T, Bassi C, Rouleau S, Le Crugel S, Moal V, Boux de Casson F, Coutant R, Mirebeau-Prunier D, Reynier P, Homedan C. Pituitarystalk interruption syndrome: a rare and severe cause of pituitarydeficiencyLaboratorydiagnosis of a newborn case. Ann BiolClin (Paris). 2017 Apr 1;75(2):215-221. English. doi: 10.1684/abc.2017.1222. PMID: 28251898.
7. Wang W, Wang S, Jiang Y, Yan F, Su T, Zhou W, Jiang L, Zhang Y, Ning G. Relationship between pituitary stalk (PS) visibility and the severity of hormone deficiencies: PS interruption syndrome revisited. ClinEndocrinol (Oxf). 2015 Sep;83(3):369-76. doi: 10.1111/cen.12788. Epub 2015 May 7. PMID: 25845766.
8. Bar C, Zadro C, Diene G, Oliver I, Pienkowski C, Jouret B, Cartault A, Ajaltouni Z, Salles JP, Sevely A, Tauber M, Edouard T. Pituitary Stalk Interruption Syndrome from Infancy to Adulthood: Clinical, Hormonal, and Radiological Assessment According to the Initial Presentation. PLoS One. 2015 Nov 12;10(11):e0142354. doi: 10.1371/journal.pone.0142354. PMID: 26562670; PMCID: PMC4643020.
9. El Chehadeh S, Bensignor C, de Monléon JV, Méjean N, Huet F. The pituitary stalk interruption syndrome: endocrine features and benefits of growth hormone therapy. Ann Endocrinol (Paris). 2010 Mar;71(2):102-10. doi: 10.1016/j.ando.2009.11.007. Epub 2009 Dec 30. PMID: 20044069.
10. Wang Q, Meng X, Sun Y, Liu F, Xu C, Qiao Y, Yang J, Li G, Wang Y. Hypoglycemia and jaundice in newborns with pituitary stalk interruption syndrome. Medicine (Baltimore). 2021 May 14;100(19):e25843. doi: 10.1097/MD.0000000000025843. PMID: 34106625; PMCID: PMC8133236.
11. Grammatikopoulos T, Deheragoda M, Strautnieks S, Neves Souza L, Hinds R, Thompson RJ, Hadzic N. Reduced Hepatocellular Expression of Canalicular Transport Proteins in Infants with Neonatal Cholestasis and Congenital Hypopituitarism. J Pediatr. 2018 Sep;200:181-187. doi: 10.1016/j.jpeds.2018.05.009. Epub 2018 Jun 20. PMID: 29935878.
12. Schneider HJ, Aimaretti G, Kreitschmann-Andermahr I, Stalla GK, Ghigo E. Hypopituitarism. Lancet. 2007 Apr 28;369(9571):1461-1470. doi: 10.1016/S0140-6736(07)60673-4. PMID: 17467517.
13. Voutetakis A, Sertedaki A, Dacou-Voutetakis C. Pituitarystalk interruption syndrome: cause, clinical manifestations, diagnosis, and management. CurrOpinPediatr. 2016 Aug;28(4):545-50. doi: 10.1097/MOP.0000000000000378. PMID: 27386973.
14. El Qadiry R, Ouayad A, Nassih H, Bourrahouat A, Ait Sab I. Neonatal Cholestasis: A Rare and Unusual Presentation of Pituitary Stalk Interruption Syndrome. Case Rep Endocrinol. 2021 May 22;2021:6161508. doi: 10.1155/2021/6161508. PMID: 36720102; PMCID: PMC8166483.