

Multiple Pituitary Hormone Deficiency in a Neonate - Clinical Presentation and Management

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Received: September 01, 2020; **Published:** September 24, 2020

Abstract

Neonatal multiple pituitary hormone deficiency is a rare occurrence resulting from congenital developmental defects of the pituitary gland and perinatal and neonatal insults. The incidence of congenital hypopituitarism is estimated to be between 1/4000 - 1/10,000. In the neonate, the clinical presentation is often non-specific and findings of hypopituitarism are not obvious. Nevertheless, pediatricians must have a high index of suspicion to focus on clues so as to not miss the diagnosis, because early initiation of appropriate treatment is key to successful management of the problem. Herein, we describe the clinical course of a neonate, who presented with micro-phallus and hypoglycemia that led to clinical suspicion and consequently a diagnosis of hypopituitarism was made. The neonate was appropriately investigated and started on hormone replacement therapy under the guidance of a pediatric endocrinologist and is making good progress. We also discuss important aspects of management of such cases, with special emphasis on hormone replacement and the sick day management.

Keywords: *Micro-Phallus; Neonatal Hypopituitarism; Hypothyroidism; Prolonged Jaundice; Hormone Replacement; Sick Day Management*

Introduction

Neonatal multiple pituitary hormone deficiency is a rare occurrence resulting from congenital developmental defects of the pituitary gland and perinatal and neonatal insults.

Case Description

We describe the case of a term baby with birth weight of 2.9 kg, born by Cesarean Section to a G3P2 mother. Parents were non-consanguineous and the other two siblings were reported to be healthy. The baby was admitted in the neonatal unit of a private hospital in Dubai, United Arab Emirates for respiratory distress necessitating high flow nasal oxygen therapy. Chest X-ray was suggestive of transient tachypnoea of newborn. The initial blood glucose level was 26 mg/dL at 1 hour of age and it normalized on intravenous fluids. Once the respiratory distress resolved by 24 hours, the baby was started on feeds and progressed to full feeds. Blood glucose was maintained on

full feeds. Systemic examination revealed micropenis with stretched penis length of 1.1 cm (Figure 1) and although testes were palpable bilaterally, the scrotum was hypoplastic and testes were high in the scrotum.



Figure 1: Micropenis (pretreatment).

Consultation with a Pediatric Endocrinologist was obtained. Ultrasound brain was normal and ultrasound abdomen confirmed a normal study with absence of Mullerian structures. Serum electrolytes were normal. Serum cortisol was very low, and follicle stimulating hormone (FSH), luteinizing hormone (LH) and testosterone levels were all low. Free thyroxine (fT4) was low, 9.4 pmol/L (normal range 11 - 32 pmol/L) and thyroid stimulating hormone (TSH) level was 4 mU/L (normal 0.27 - 4.2 mU/L). TSH was inappropriately normal for the low free T4. Adrenocorticotrophic hormone (ACTH) was low (4.2 pg/ml, normal > 7.2 pg/ml). ACTH stimulation test was performed and was abnormal (peak cortisol 45 and 47 nmol/L at 30 and 60 minutes, almost same as at baseline). Luteinizing hormone releasing hormone (LHRH) stimulation test showed flat response of LH and FSH following LHRH injection. Liver function tests carried out on day 6 revealed total bilirubin 9.9 mg/dL, direct bilirubin 2.2 mg/dL (raised), AST 87.5 IU (slightly raised) and the rest of the results normal. Ophthalmology review was normal with no evidence of optic nerve hypoplasia. Magnetic resonance imaging (MRI) of the brain showed small sella turcica with hypoplastic pituitary gland. Ectopic posterior pituitary bright spot was observed in supraoptic space and the pituitary stalk was not visualized (Figure 2).

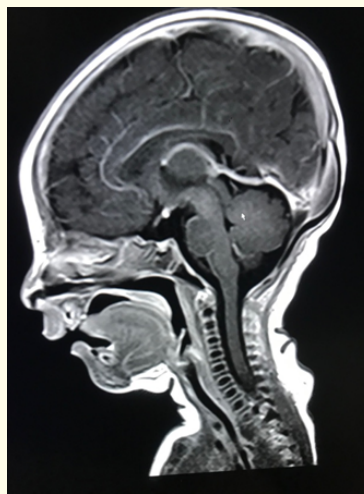


Figure 2: MRI brain showing above findings

The baby had relative hypotonia with slow progression on suck feeds. Transfer out of neonatal unit was only possible by day 6 due to above mentioned reasons as well as temperature instability. He was initiated on Hydrocortisone (11 mg/m² per day in 3 divided doses). After 24 hours on hydrocortisone, the baby was started on Thyroxine 25 microgram once daily. He was then discharged and parents were provided with a written plan on emergency management in case of illness and training on use of intramuscular (IM) hydrocortisone in emergencies.

At follow up on day 16, the free T4 had normalized but the jaundice (both total and direct bilirubin) worsened. Hydrocortisone dose was increased to 13 mg/ m² per day and subsequently, the jaundice resolved within a week. He received the first dose of injection testosterone 25 mg at 1 month of age and 2 further doses at monthly intervals. There was a good response and the stretched penis length crossed 3.5 cm (Figure 3). He is currently around 8 months of age and has weight on 9th centile with height at 0.4th centile. The parents were advised of possible growth hormone deficiency which needs further evaluation later and the possibility of needing growth hormone treatment His developmental milestones are progressing well and his follow up results are stable, maintaining the thyroxine and hydrocortisone replacement doses.



Figure 3: After first dose of testosterone.

Discussion

The pituitary gland is essential for regulation of growth, metabolism, reproduction and homeostasis. It consists of adenohypophysis anteriorly and neurohypophysis posteriorly. Growth hormone (GH), follicle stimulating hormone (FSH), luteinizing hormone (LH), thyroid stimulating hormone (TSH), prolactin (PRL) and adrenocorticotrophic hormone (ACTH) are released from the anterior lobe and arginine vasopressin (AVP) and oxytocin from the posterior lobe [1]. Neonatal hypopituitarism with an incidence of around 1 in 4000 - 10,000 births [2] may occur due to developmental defects of the pituitary gland, genetic mutations, and perinatal and neonatal events.

The affected babies usually have normal height and weight at birth. The clinical findings may relate to deficiency of the pituitary hormones, and findings like midline defects or ocular defects (septo-optic dysplasia), corpus callosum agenesis may be noted as well. About 20 - 25% babies may present with hypoglycemia, hyponatremia or recurrent infections [3]. Cortisol deficiency can lead to fluid overload, hypoglycemia, hyponatremia and even heart failure [4,5] which can be managed by replacing hydrocortisone and correcting hypothyroidism. Prolonged jaundice and cholestasis may be noted [6] and it tends to resolve soon if treatment is started early. Temperature instability and prolonged jaundice may be due to the TSH deficiency as well. Rarely, central diabetes insipidus can be a presenting feature with

polyuria, hypernatremia and dehydration. In females, genital development is not affected, but in males, micro-phallus may be a feature. Micropenis is defined as stretched penile length less than 2.5 standard deviation below the mean (values under 1.5 cm at gestational age 30 weeks, 2 cm at 34 weeks and under 2.5 cm in term infants) [7].

Congenital causes [8] including congenital infections (syphilis, toxoplasmosis), hypothalamus-pituitary development defects, midline defects, cleft lip/palate and genetic mutations-a number of distinct mutations have been reported but are beyond the scope of discussion for this article [8]. Perinatal-neonatal causes include birth trauma-asphyxia (neonatal sepsis and hemochromatosis (transient)).

The clinical evaluation requires a detailed history including questions related to above causes, and physical examination focused on fontanelle size, eyes, cleft palate/lip, hepato-splenomegaly, lymphadenopathy, jaundice and malformations. Presence of micropenis and undescended testicles are to be noted in the genital examination [1,8].

Diagnostic evaluation includes testing for the hormone deficiencies including cortisol, ACTH, thyroid function tests, FSH, LH, testosterone levels along with blood glucose, liver function tests and serum electrolytes. Growth hormone levels may be high in newborns and testing can be deferred to a later age as decided by the endocrinologist. Imaging is very important to assess the anatomic details including pituitary gland height, ectopic posterior pituitary, infundibulum morphology, absence of corpus callosum and of septum pellucidum, anatomy of optic nerve and chiasma, presence of holoprosencephaly, schizencephaly, cerebellar hypoplasia, absence of fornix and presence of Chiari malformation [9,10]. Genetic studies should be targeted based on family history and other features [11,12].

Treatment involves multidisciplinary input with hormone replacement and regular follow up. Treatment of central hypothyroidism is initiated with 6 - 8 microgram/kg/day L-thyroxine, aiming to keep the free T4 level in the upper part of the normal range [13]. It is vital to determine the cortisol level before thyroxine replacement, since an increase in cortisol clearance can result in cortisol deficiency when thyroxine is administered to infants with low cortisol level [14]. In cases of cortisol deficiency, oral hydrocortisone should be started first and thyroid replacement should be initiated subsequently. Oral cortisol dose should be given by dividing into three doses of 12/m²/day (higher dose in the morning). In infants with cholestasis at initiation of treatment, oral thyroxine and hydrocortisone should be administered at higher doses due to absorption deficiency with the caveat that the doses be decreased once cholestasis resolves [15]. Diabetes insipidus may be unmasked with hydrocortisone treatment as the free water load is cleared [16] and the infant should be observed closely, particularly in cases where the neurohypophysis brightness is not visualised on MRI. Testosterone injection, dihydrotestosterone gel application or recombinant human gonadotropin subcutaneous infusion treatments can be initiated between the ages of 1 - 6 months in boys with diagnosis of hypogonadotropic hypogonadism (HH) [17]. Acceptable results have been obtained with 25 mg depot testosterone intramuscularly, every three weeks over a period of three months [18].

All pediatricians must be well aware of stress dosing with hydrocortisone for patients on steroid replacement therapy. If the child has a mild inter-current illness such as respiratory or ear infection with no fever, or has suffered minor falls, cuts or bruises, there is no need to increase the hydrocortisone dose. However, if the child is unwell with fever and reduced activity (e.g. fever > 38°C, diarrhea, vomiting or moderate injury), but is able to tolerate oral medication, double or triple dose of steroids is needed. If the baby is unable to tolerate oral medication or is unconscious, an intramuscular injection of hydrocortisone must be given and the baby taken to the emergency department (parents must be instructed to keep this medication at home and should be trained to administer it if required). In the emergency department, if the child is severely unwell, unresponsive or vomiting, check for blood sugar, urea and electrolytes. Intravenous hydrocortisone should be commenced and continued till the child improves and is able to tolerate oral medication. Blood glucose monitoring, and intravenous fluid management are vital. Double dose hydrocortisone therapy can be started once the child is able to tolerate oral medications. Any surgery would necessitate stress dosing pre and peri-operatively.

Conclusion

Clinicians should have a high index of suspicion while examining and managing neonates with micro-phallus and hypoglycemia so as to not miss hypopituitarism. Multidisciplinary input and stress on parent education are important with emphasis on compliance with hormone replacement. Parents should be made aware of stress dosing schedule and should be provided with a written plan and adequate training. The child may need growth hormone treatment in the future, and pubertal induction would be required later. Prognosis is good provided good compliance and regular monitoring are ensured.

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Volume 9 Issue 10 October 2020

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