Neonatal Hypopituitarism: Diagnosis and Treatment Approaches

Running short title: Neonatal Hypopituitarism

Selim Kurtoğlu1,2, Ahmet Özdemir1, Nihal Hatipoğlu2

1Erciyes University, Faculty of Medicine, Department of Pediatrics, Division of Neonatology
2Erciyes University, Faculty of Medicine, Department of Pediatrics, Division of Pediatric Endocrinology

Corresponding author: Ahmet Özdemir MD, Department of Pediatrics, Division of Neonatology, Erciyes University Medical Faculty, Kayseri, Turkey
E-mail: dr.ozdemir@yahoo.com
Tel: 00-90-3522076666
Fax: 00-90-3524375825

Received: 01.02.2018
Accepted: 08.05.2018

What is already known on this topic?
The pituitary gland is the central regulator of growth, metabolism, reproduction and homeostasis. Hypopituitarism is defined as a decreased release of hypophysis hormones, which may be caused by pituitary gland disease or hypothalamus disease. Clinical findings for neonatal hypopituitarism depend on causes and hormonal deficiency type and degree. If early diagnosis is not made, it may cause pituitary hormone deficiencies.

What this study adds?
We aim to contribute to the literature through a review of etiological factors, clinical findings, diagnoses and treatment approaches for neonatal hypopituitarism. We also aim to increase awareness of neonatal hypopituitarism. We also want to emphasize the importance of early recognition.

Abstract
Hypopituitarism is defined as a decreased release of hypophysis hormones, which may be caused by pituitary gland disease or hypothalamus disease. Clinical findings for neonatal hypopituitarism depend on causes and hormonal deficiency type and degree. Patients may be asymptomatic or may demonstrate non-specific symptoms, but may still be under risk for development of hypophysis hormone deficiency with time. Anamnesis, physical examination, endocrinological, radiological and genetic evaluations are all important for early diagnosis and treatment. Treatment of hypopituitarism patients is possible through treatment of hypophysis and hypothalamus disorders. The aim of this article is to contribute to the literature through a review of etiological factors, clinical findings, diagnoses and treatment approaches for neonatal hypopituitarism.

Keywords: Diagnosis, hypophysis, hypothalamus, neonatal hypopituitarism, treatment

Introduction
The pituitary gland is the central regulator of growth, metabolism, reproduction and homeostasis. It consists of the frontal lobe (adenohypophysis), the posterior lobe (neurohypophysis) and the middle lobe. GH, FSH, LH, TSH, PRL, and ACTH are released from the frontal lobe and AVP and oxytocin from the posterior lobe. The frontal and middle lobes consist of ectoderm and the posterior lobe consists of neural ectoderm (1). A series of transcription factors are involved in pituitary gland formation. Neonatal hypopituitarism may occur due to developmental defects of the pituitary gland, genetic mutations, and perinatal and neonatal events (1-8) (Table 1). Genetic mutations causing hypopituitarism and their sub-groups are shown in Tables 2 and 3 (1,9-14). The incidence of congenital hypopituitarism is estimated to be between 1/4000-1/10,000 (15). Hypopituitarism findings may not be present in the neonatal period and may occur with different non-specific clinical presentations. Also, the sensitivity of laboratory methods may not be satisfactory for newborns (13). Nevertheless, it is possible for neonatology specialists to reach a diagnosis by focusing on some clues.

Neonatal Clinical Findings in Congenital Hypopituitarism Cases
It is interesting that congenital hypopituitary newborns have normal birth weight and height (16). Clinical presentations in hypopituitary newborns occur due to deficient hormones or due to combined or total hypophyseal hormone deficiency. Ocular findings, midline defects and genital abnormalities can be detected in patients (Figures 1-3). Generally, non-specific findings are observed. Clinical findings may become evident in asymptomatic patients with time. Observation is required in the neonatal period for optic nerve hypoplasia, midline defects or
syndromes, even though initial endocrinol evaluations are normal (17-19). Diagnosis is difficult due to the problems faced with premature infants, hypothalamus-pituitary axis immaturity, limited information on normal values for newborns and contraindicated stimulation tests. It is reported that only 23% of cases are diagnosed with postnatal problems, such as hypoglycemia, hyponatremia or recurrent sepsis in the neonatal period (20). Non-specific symptoms such as hypoglycemia, neuroglycopenia-related lethargy, apnea, jitteriness, convulsion, inability to gain weight, hyponatremia unaccompanied by hyperpotassemia, temperature instability, recurrent sepsis, hemodynamic instability, neonatal cholestasis and prolonged jaundice are observed in the neonatal period (21-23). In addition to hypoglycemia, lack of thymic involution and fluid intolerance are striking in cortisol deficiency (24). Cortisol deficiency-related hypoglycemia as the result of isolated or combined type ACTH deficiency is severe. Hypoglycemia may occur in isolated growth hormone deficiency. Heart failure constituting a vital risk in newborns with the LHX4 mutation related multiple hormone deficiency and heart failure can be cured with thyroxine and hydrocortisone treatment, and hypoglycemia can be cured with growth hormone treatment (25). Cortisol increases bile flow and problems occur in bile acid synthesis and transport with cortisol deficiency and cholestasis occurs. Cholestasis occurs generally in the first 13 days. Transaminases increase after 2-4 weeks but GGT remains in normal ranges (26). Liver biopsy is performed before hypopituitarism diagnosis in cholestasis cases and canaliculoc cholestasis and mild portal eosinophilic infiltration is detected in its histopathology. If there is a delay in diagnosis, transaminases continue to increase, while cholestasis recovers in 6-10 weeks if treatment is started after diagnosis (27,28). There is ACTH deficiency in more than 50% of the cases with eye and frontal brain abnormalities. Temperature instability and prolonged physiological jaundice is present in cases with neonatal TSH deficiency. The development of female genitalia is independent of hormone secretion; hence congenital hypogonadotropic hypogonadism is not expected to affect the normal development of female external genitalia (29). Micropenis is defined according to a 2.2 SD border value from the mean value. Values below 1.5 cm at thirty weeks old, 2 cm at 34 weeks old and below 2.5 cm in term infants are considered as micropenis (30). Optic nerve hypoplasia or corpus callosum agenesis related nystagmus may be observed in infants (31,32). Polyhydramnios, polyuria, weight loss, anxiety, water demand instead of formula, dehydration findings and hypernatremia are observed in diabetes insipidus cases (33).

Diagnostic Approaches in Neonatal Hypopituitarism

1. Patient and Familial History: Consanguineous marriage, index cases, traumatic/breech birth and neonatal central nervous system infections are questioned.

2. Physical Examination Findings and Symptoms: Height, weight and head circumference are measured in newborns. Fontanela, eye examination, cleft palate/lip, hepatosplenomegaly, lymphadenopathy, jaundice and malformations are examined. Presence of microphallus and descended testicle are noted in the genital examination.

Syndromes accompanied by hypophysyal deficiency are investigated (1) (Table 4).

3. Endocrine Evaluation:
   a. Pituitary - Adrenal Axis Evaluation: ACTH deficiency causes life threatening results. Quick action is important especially with asymptomatic midline defects. Circadian rhythm is not thorough mature in cortisol secretion in the first six postnatal months. Thus, cortisol should be measured every hour of the day instead of only in the morning (34). Mehta A et al interpret cortisol values below 175 nmol/L (6.34 microgram/dl) at 8 o’clock in the morning as deficiency (21). Multiple random cortisol measurements are not suitable for premature and ill infants and cortisol measurement by creating hypoglycemia is not recommended. But cortisol measurement may be useful in addition to insulin and growth hormone measurement in infants with hypoglycemia presentation. Cortisol deficiency is present if cortisol response remains below 12.67 micrograms/dl in hypocorticaly infants (35). Even though a standard ACTH test is easy and safe, its sensitivity is approximately 80%-90%. (36). False negative results can occur even though the infant has ACTH deficiency (36). CRH test can be done in order to determine ACTH deficiency in infants. But normal values are not present for central hypothyroidism and midline defects and it is contraindicated in ill and infants (37). When the cortisol value at 8 o’clock in the morning is detected as 175 nmol/L (6.34 micrograms/dl) as the circadian rhythm matures, ACTH deficiency can be excluded if the cortisol level is above 540 nmol/L (19.56 microgram/dl) in the 30h minute with a low dose ACTH test. The specificity of the test was found to be 100% and the sensitivity to be 69%-70%.
   b. TSH Deficiency: In central hypothyroidism cases, low or normal TSH level despite a low FT4 level is striking. Central thyroidism is diagnosed if the free T4 level is below 0.8 ng/dl and TSH is normal or slightly high (38). It should be kept in mind that severe infection, patient thyroid syndrome or dopamine infusion can cause low TSH levels in infants (39). Early diagnosis is important in central hypothyroidism cases since 78% of other hormone deficiencies can accompany it (1). Hypoglycemia and neonatal hepatitis develop if hypothyroidism is diagnosed late and mortality increases to nearly 14% (36). The necessity of a TRH test for diagnosis is controversial (40, 41).
c. Gonadotropin Deficiency: Detection of micropenis alone or together with undescended testicle in boys is observed in isolated hypogonadotropic hypogonadism or multiple hypophysial hormone deficiencies. Secretion of postnatal FSH and LH occurs in normal male newborns and testosterone levels increase with a peak in the 4-10th weeks and stop to decrease around the sixth month. High gonadotropin levels may last up to two years in girls. This series of events is called mini-puberty (42). If LH is < 0.8 IU/L and total testosterone is < 30 ng/dl in male infants between postnatal 15 days-6 months, central hypogonadism is diagnosed (43). In female infants central hypogonadism is diagnosed if FSH is < 1.0 IU/L between 15 days-2 years (44-47). Hypogonadotropic hypogonadism can be diagnosed with GnRH and hCG tests in infants (48,49). Basal FSH and LH are low in infants with hypogonadotropic hypogonadism and a blunt gonadotropin response is seen after the test (37). Attention should be paid to penile growth and testicular descent in infants tested for human chorionic gonadotropin (50).

c. Growth Hormone Deficiency: It should be kept in mind that growth hormone level is high in the neonatal period (51,52). Growth hormone can be measured directly in the neonatal period. But a decrease in the growth hormone level and an increase in IGF-1 and IGFBP-3 levels are observed in the neonatal period starting from birth. Kurtoglu et al stated that growth hormone, IGF-1 and IGFBP-3 levels changed in term infants compared to postnatal weeks. Growth hormone levels decreased and IGF-1 and IGFBP-3 levels increased gradually (53). (Table 5). In the study by Binder G et al, growth hormone levels measured on filter paper in the neonatal period for children for whom growth hormone deficiency was detected at later ages were studied retrospectively and it was observed that in the postnatal first week, a level of 7 ng/ml reflected growth hormone deficiency and this level showed 100% sensitivity and 98% specificity (54). The same group also observed that neonatal growth hormone deficiency was present in cases that had multiple hormone deficiency and malformations but that isolated growth hormone deficiency was not detected in newborns (55). It is also emphasized that random growth hormone measurement is useful in the first 14 days in newborns (56).

Growth hormone stimulation tests are not recommended in infants under 12 months old. But growth hormone levels measured in infants with hypoglycemia may give an idea, though its specificity has a low ratio (57,58). A growth hormone value < 7.7 ng/ml in infants with hypoglycemia is suggested as a growth hormone deficiency criteria (35). Some researchers reported that a glucagon stimulation test may be used under 12 months old. When glucagon is injected at a dose of 0.03 mg/kg and samples are taken at basal, 45, 90, 120, 150 and 180 minutes, the growth hormone level is normally expected to be above 10 ng/ml (59).

e. Prolactin Deficiency: Prolactin level is low in cases with POU1F1, LHX3, OTX2 and IGFSF-1 mutations and in cases of panhypopituitarism. Values below 37 ng/ml in the postnatal first 30 days and 24 ng/ml between the 30-60th days are accepted as hypoprolactinemia (60). Breast tissue should not be palpated before taking blood and it should be questioned whether any medicine affecting prolactin level has been taken. Prolactin levels are low in infants given dopamine as an inotropic agent in the neonatal period (61).

f. Diabetes Insipidus: The definition for polyuria in diabetes insipidus is a daily urine amount above 2 liters/m2, which is equal to the urine amount at birth being over 150 ml/kg/day (62). The suggested criterion of 4 ml/kg/h in children for polyuria is taken as a urine amount of over 6 ml/kg/hour in the neonatal period (63). In most cases of diabetes insipidus presentation in the neonatal period, anatomical defects or autosomal dominant-recessive genetic causes are present. Central insipidus presentation is clear in septo-optic dysplasia, corpus callosum agenesis and holoprosencephaly cases (64). More rarely, posterior hypophysis located tumours and craniopharyngioma operation may be the cause for diabetes insipidus. Symptoms such as polyuria, polydypsia (excessive water drinking instead of formula), weight loss, growth deficiency and persistent hypernatremia despite giving fluid and diluted urine are striking. Plasma and urine osmolality measurements in the early hours of the morning bring us closer to a diagnosis (1). Serum osmolality <270 mosm/kg and urine osmolality >600 mosm/kg draw us away from a diagnosis of diabetes insipidus. A water restriction test is risky in the neonatal period and can only be done in special centers (33). A nasal desmopressin test can be done. On the 8th and 24th hours after the application of 0.012 ml of desmopressin (1 ml=100 microgram), observation of a decrease in serum sodium and osmolality, an increase in urine osmolality and a decrease in diuresis support the diagnosis (65).

4. Radiological Examinations: Bone age is detected with knee graphy and epiphyseal dysgenesis is investigated. Brain and hypophysis imaging should be done in infants considered to have hypopituitarism, with the severity of the cases paralleling neuro-radiological abnormalities (18). Pituitary gland height, neurohypophysis brightness/ectopia, undescended posterior lobe, infundibulum morphology, absence of corpus callosum and septum pellucidum, optic nerve and chiasma, holoprosencephaly, schizencephaly, cerebellar hypoplasia, absence of fornix and Chiari malformation are noted with imaging (66). Lack of neurohypophysis brightness supports the diagnosis in central diabetes insipidus cases. Studies on pituitary gland height in newborns are presented in Table 6 (67-70).

5. Genetic Studies: Genetic studies are planned according to familial history, physical examination, laboratory and radiological findings (13,15).

Treatment Approaches and Follow-up in Neonatal Hypopituitarism
Cases diagnosed to have neonatal hypopituitarism should be followed-up by a multidisciplinary team. Suitable hormonal treatments, providing follow-up by considering that some hormone deficiencies will occur with time, vision and neurodevelopmental follow-up in syndromic cases, acquisition of genetic data and conversations with the family are important during follow-up.

Central hypothyroidism treatment is started with 6-8 microgram/kg/day L-thyroxine. The aim is to keep the free T4 level in the upper part of the normal range. Dose deficiency is determined by free T4 and overdose by free T3 level (71). It is important to know the cortisol level before thyroid replacement. Cortisol clearance increases and cortisol deficiency occurs when thyroidine is given to infants with low cortisol level and especially in preterm cases (72). Hydrocortisone should be started first in these cases and then thyroid replacement should be done.

Oral hydrocortisone is started in cortisol deficiency cases. In preterm infants, daily cortisol production is determined as 7.28 mg/m2/day on the fifth day and 6 mg/m2/day in the second week (73). Oral cortisol should be higher than daily production and should be given by dividing into three doses of 12-18 mg/m2/day. In case of stress, the dose is multiplied by 2-3. Masked diabetes insipidus may occur with hydrocortisone treatment and the infant should be observed (33). Oral thyroxine and hydrocortisone doses are kept high in infants with cholestasis at the beginning due to absorption deficiency and it should be kept in mind that the doses should be decreased after cholestasis is resolved (74).

Testosterone injection, dihydrotestosterone gel application or recombinant human gonadotropin subcutaneous infusion treatments can be done between the 1st-6th months in boys in whom hypogonadotropic hypogonadism is detected (30, 75, 76). Testosterone is applied in four doses of 25 mg once every three weeks (77).

Intranasal or peroral desmopressin is used in central diabetes insipidus cases. The maximum plasma concentration is provided in 40-55 minutes with intranasal or oral use, the half-life is nearly 3.5 hours, urine output starts to decrease in 1-2 hours and its effect lasts 6-18 hours (78). It is recommended to start treatment with a low dose and titrate according to the response. The intranasal form should be started with a dose of 0.05-0.1 micrograms and titrated (79). Oral tablets are dissolved in 3-5 ml of water and given by dividing the daily dose of 5 micrograms/kg into two (80,81). When the treatment is started, the daily liquid intake should be lowered to maintenance fluid due to hyponatremia risk (65,80).

Growth hormone treatment can be started in the neonatal period. Treatment is often started after the neonatal period since diagnosis is generally delayed. Growth hormone treatment can contribute to hypoglycemia recovery (16).

Authorship Contributions

Financial Disclosure: The authors declared that this study received no financial support.

Conflict of Interest: No potential conflict of interest was reported by the authors.

References


Figure 1: Facial appearance in the presence of neonatal growth hormone deficiency (from Erciyes University Faculty of Medicine Neonatology Department).

Figure 2: Midline defect with cleft palate-lip and micropenis (from Erciyes University Faculty of Medicine Neonatology Department)
Figure 3: A case of holoprosencephaly with cleft palate / lip, anterior and posterior pituitary insufficiency (from Erciyes University Faculty of Medicine Neonatology Department)

Table 1: Causes of neonatal hypopituitarism

<table>
<thead>
<tr>
<th><strong>Congenital Causes</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal hyperglycaemia</td>
<td></td>
</tr>
<tr>
<td>Congenital infections (syphilis, toxoplasmosis)</td>
<td></td>
</tr>
<tr>
<td>Hypothalamus-pituitary development defects</td>
<td></td>
</tr>
<tr>
<td>Midline defects / cleft palate, lip</td>
<td></td>
</tr>
<tr>
<td>Genetic mutations</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Perinatal-Neonatal Causes</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth trauma-asphyxia (pituitary stalk junction)</td>
<td></td>
</tr>
<tr>
<td>Neonatal sepsis</td>
<td></td>
</tr>
<tr>
<td>Hemochromatosis (transient)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2: Mutations and characteristics in genes involved in pituitary gland development

<table>
<thead>
<tr>
<th><strong>Transcription factor</strong></th>
<th><strong>Type of inheritance</strong></th>
<th><strong>Hormone deficiencies</strong></th>
<th><strong>MRI findings</strong></th>
<th><strong>Other findings</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>POU1FI (PIT-1)</td>
<td>OR, OD</td>
<td>GH, TSH, PRL</td>
<td>APH</td>
<td></td>
</tr>
<tr>
<td>PROP1</td>
<td>OR</td>
<td>GH, TSH, LH, FSH, PRL</td>
<td>APH, E</td>
<td>Transient AP hyperplasia</td>
</tr>
<tr>
<td>HESX1</td>
<td>OR, OD</td>
<td>IGHE, KPHE</td>
<td>APH, EPP</td>
<td>Septo-optic dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Corpus callosum agenesis</td>
</tr>
<tr>
<td>LHX3</td>
<td>OR</td>
<td>GH, TSH, LH, FSH, PRL</td>
<td>APH, N, E</td>
<td>Neck rotation limited,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Short cervical spin,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sensorineural deafness</td>
</tr>
<tr>
<td>LHX4</td>
<td>OD</td>
<td>GH, TSH, ACTH, in addition FSH, LH be found</td>
<td>APH, EPP</td>
<td>Cerebellar anomalies</td>
</tr>
<tr>
<td>SOX2</td>
<td>OD (de novo)</td>
<td>HH, GH deficiency</td>
<td>APH</td>
<td>Anophthalmia, microphthalmia, oesophageal atresia, genital tract anomalies, hypothalamic hamartoma, diplegia, sensorineural deafness</td>
</tr>
<tr>
<td>SOX3</td>
<td>X-linked</td>
<td>Isolated or combined</td>
<td>APH, EPP</td>
<td>Mental retardation</td>
</tr>
</tbody>
</table>
**Table 3: Isolated growth hormone deficiency subtypes**

<table>
<thead>
<tr>
<th>Type</th>
<th>Gene</th>
<th>Heredity</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>GH1</td>
<td>OR</td>
<td>Postnatal severe growth failure, very low GH level, antibody development with treatment</td>
</tr>
<tr>
<td>IB</td>
<td>GH1, GHRHR</td>
<td>OR</td>
<td>Lighter growth insufficiency, GH is present but no antibody is formed by treatment</td>
</tr>
<tr>
<td>II</td>
<td>GH1</td>
<td>OD</td>
<td>Different growth insufficiency table, normal, hypoplastic pituitary gland, other hormone deficiencies may be added</td>
</tr>
<tr>
<td>III</td>
<td>BTK, SOX3 or other genes?</td>
<td>X-linked</td>
<td>Agammaglobulinemia and mental retardation are accompany</td>
</tr>
</tbody>
</table>

**Table 4: Some syndromes with pituitary insufficiency**

**PHACE(S)**
- Posterior fossa anomalies (Dandy-Walker cyst), hemangiomas of the face and neck, arterial malformations, cardiac defects, eye anomalies, sternal defects (Sternal cleft, supraumbilical raphe)

**RIEGER**
- Malformations in the anterior chamber of the eye, preumbilical umbilicus, abnormal teeth, mental retardation

**Johanson-Blizzard Syndrome**
- Microcephaly, exocrine pancreatic dysfunction, recto-urethral anomalies, hypothyroidism

**Pallister-Hall Syndrome**
- Polydactyly, imperfore anus, hypothalamic hamartoblastoma

**Table 5: Weekly growth hormone (GH), IGF-1 and IGFBP-3 values in the neonatal period**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0-7 days</th>
<th>8-14 days</th>
<th>15-21 days</th>
<th>22-30 days</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GH (ng/ml)</td>
<td>13.6±5.68</td>
<td>9.38±4.06</td>
<td>8.73±3.19</td>
<td>7.91±5.57</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IGF-1 (ng/ml)</td>
<td>55.4±49.6</td>
<td>69.6±46.6</td>
<td>82.3±70.0</td>
<td>89.5±47.6</td>
<td>&lt; 0.026</td>
</tr>
<tr>
<td>IGFBP-3 (ng/ml)</td>
<td>2043±572.0</td>
<td>2352±777.0</td>
<td>3002±856.0</td>
<td>3133±1150.0</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**Table 6: Neonatal period pituitary gland height values (mm)**
<table>
<thead>
<tr>
<th>Researcher</th>
<th>n number and age</th>
<th>Pituitary Gland Height</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kitamura E et al (67)</td>
<td>88 (0-122 day)</td>
<td>3.9±0.7 mm</td>
</tr>
<tr>
<td>Dietrich RB et al (68)</td>
<td>17 (0.1-1.5 week)</td>
<td>4.12±1.13 mm</td>
</tr>
<tr>
<td></td>
<td>17 (1.7-6.0 week)</td>
<td>3.94±0.6 mm</td>
</tr>
<tr>
<td>Agyropoulou M et al (69)</td>
<td>12 (0-12 month)</td>
<td>3.5±0.5 mm</td>
</tr>
<tr>
<td>Sarı S et al (70)</td>
<td>14 (0-12 month)</td>
<td>Girl 3.81±0.68 mm</td>
</tr>
<tr>
<td></td>
<td>13 (0-12 month)</td>
<td>Boy 3.91±0.75 mm</td>
</tr>
</tbody>
</table>