REVIEW

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Neonatal Hypopituitarism: Approaches to Diagnosis and Treatment

Selim Kurtoğlu[1,2], Ahmet Özdemir[1], Nihal Hatipoğlu[2]

[1]Erciyes University Faculty of Medicine, Department of Pediatrics, Division of Neonatalogy, Kayseri, Turkey
[2]Erciyes University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Endocrinology, Kayseri, Turkey

Abstract

Hypopituitarism is defined as a decreased release of hypophyseal hormones, which may be caused by disease of the pituitary gland disease or hypothalamus. The clinical findings of neonatal hypopituitarism depend on the causes and on presence and extent of hormonal deficiency. Patients may be asymptomatic or may demonstrate non-specific symptoms, but may still be at risk for development of pituitary hormone deficiency over time. Patient history, physical examination, endocrinological, radiological and genetic evaluations are all important for early diagnosis and treatment. The aim of this paper was to present a review of etiological factors, clinical findings, diagnosis and treatment approaches in 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 a frontal lobe (adenohypophysis), a posterior lobe (neurohypophysis) and a middle lobe. Growth hormone (GH), follicle stimulating hormone (FSH), luteinising hormone (LH), thyroid stimulating hormone (TSH), prolactin (PRL) and adrenocorticotropic hormone (ACTH) are released from the frontal lobe and arginine vasopressin (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 (Table 1) (1,2,3,4,5,6,7,8). Genetic mutations causing hypopituitarism and their sub-groups are shown in Tables 2 and 3 (1,9,10,11,12,13,14). 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 neonatologists to reach a diagnosis by focusing on some clues.

Neonatal Clinical Findings in Congenital Hypopituitarism Cases

It is interesting that newborns with congenital hypopituitarism have normal birth weight and height (16). Clinical presentations in hypopituitary newborns occur due to combined or total hypophyseal hormone deficiency. Ocular findings, midline defects and genital abnormalities may also be detected in these patients (Figures 1, 2, 3).

Generally these patients present with non-specific findings although clinical findings may become evident over time. All newborns suspected of hypopituitarism must be assessed for optic nerve hypoplasia, midline defects or syndromes; even those in whom the initial endocrine evaluations are normal (17,18,19). In premature infants diagnosis is difficult due to problems commonly associated with prematurity including hypothalamus-pituitary axis immaturity and limited information on normal values for newborns and contraindication of 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

Address for Correspondence: Ahmet Özdemir MD, Erciyes University Faculty of Medicine, Department of Pediatrics, Division of Neonatalogy, Kayseri, Turkey
Phone: +90 352 207 66 66 **E-mail:** dr.ozdemir@yahoo.com **ORCID ID:** orcid.org/0000-0002-7572-069X

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symptoms such as hypoglycemia, neuroglycopenia-related lethargy, apnea, jitteriness, convulsions, inability to gain weight, hyponatremia unaccompanied by hyperkalemia, temperature instability, recurrent sepsis, hemodynamic instability, neonatal cholestasis and prolonged jaundice are observed in the neonatal period (21,22,23). In addition to hypoglycemia, lack of thymic involution and fluid intolerance are striking in cortisol deficiency (24). Cortisol deficiency-related hypoglycaemia, as a result of isolated or combined-type ACTH deficiency, is severe. Heart failure constitutes a vital risk in newborns with the *LHX4* mutation-related multiple hormone deficiency. Heart failure in these newborns can be resolved with thyroxine and hydrocortisone treatment and the hypoglycemia can be treated successfully with GH (25). Cortisol increases bile flow and cortisol deficiency leads to problems in bile acid synthesis and transport and eventually cholestasis. Cholestasis occurs generally in the first 13 days of life. Transaminase levels increase after 2-4 weeks but GGT remains within normal ranges (26). In cholestasis cases, liver biopsy, usually performed before hypopituitarism diagnosis, reveals canalicular cholestasis. Mild portal eosinophilic infiltration is demonstrable on histopathology. If there is a delay in diagnosis, transaminase levels continue to increase, while cholestasis recovers in 6-10 weeks if treatment is started after diagnosis (27,28). ACTH deficiency is present in over 50 % of cases with ocular and frontal brain abnormalities. Temperature instability and

Table 1. Causes of neonatal hypopituitarism

Congenital causes
Maternal hyperglycaemia,
Congenital infections (syphilis, toxoplasmosis),
Hypothalamus-pituitary development defects,
Midline defects, cleft lip/palate,
Genetic mutations.
Perinatal-neonatal causes
Birth trauma-asphyxia (pituitary stalk junction),
Neonatal sepsis,
Hemochromatosis (transient).

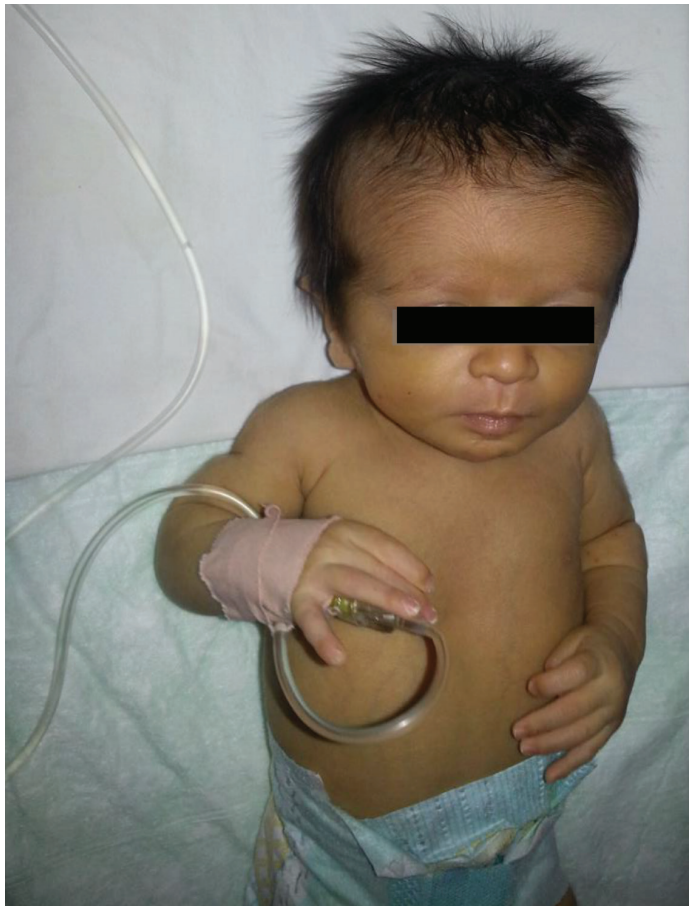

Figure 1. Facial appearance in the presence of neonatal growth hormone deficiency (from the files of Erciyes University Faculty of Medicine, Department of Neonatology)

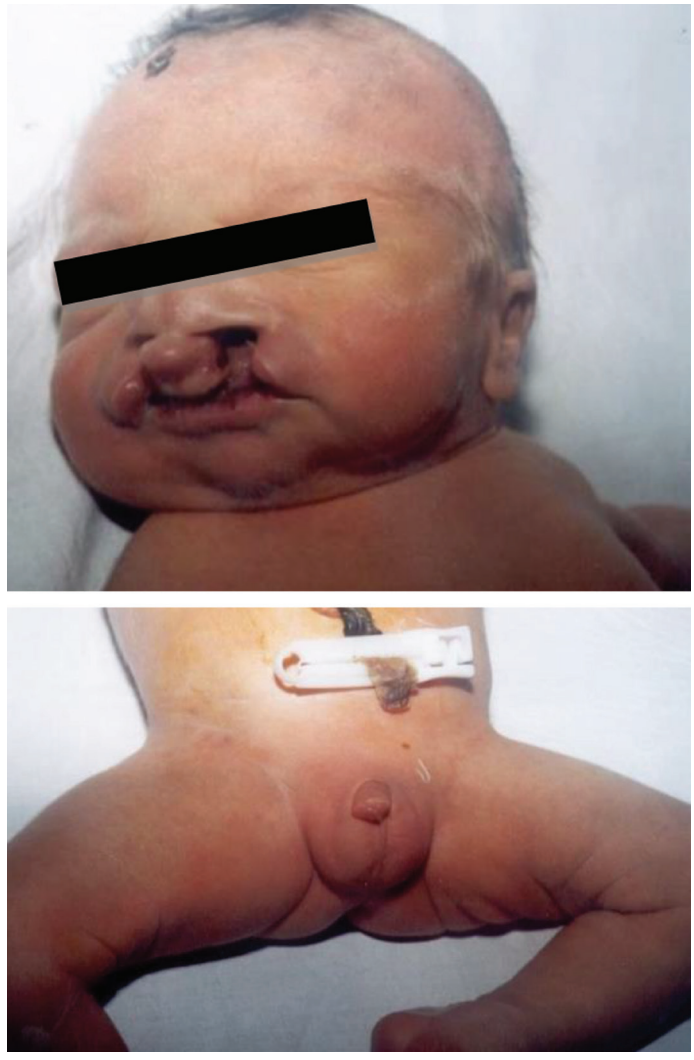

Figure 2. Midline defect with cleft palate-lip and micropenis (from the files of Erciyes University Faculty of Medicine, Department of Neonatology)

prolonged physiological jaundice are also usually present in cases with neonatal TSH deficiency. The development of female genitalia is independent of hormone secretion; hence congenital hypogonadotropic hypogonadism (HH) is not expected to affect the normal development of female external genitalia (29). Micropenis is defined according to a -2.5 standard deviation cut-off from the mean value. Values under 1.5 cm at gestational age 30 weeks, 2 cm at 34 weeks and under 2.5 cm in term infants are defined as micropenis (30). Optic nerve hypoplasia or corpus callosum agenesis-related nystagmus may be observed in infants (31,32). Polyhydramniosis, polyuria, weight loss, anxiety, demand for water instead of formula, signs and symptoms of dehydration and hypernatremia are observed in cases of diabetes insipidus (33).

Diagnostic Approaches in Neonatal Hypopituitarism

Patient and family history: A careful and detailed medical history should be obtained including information on consanguineous marriage, index cases, traumatic/breech birth and possible neonatal central nervous system infection.

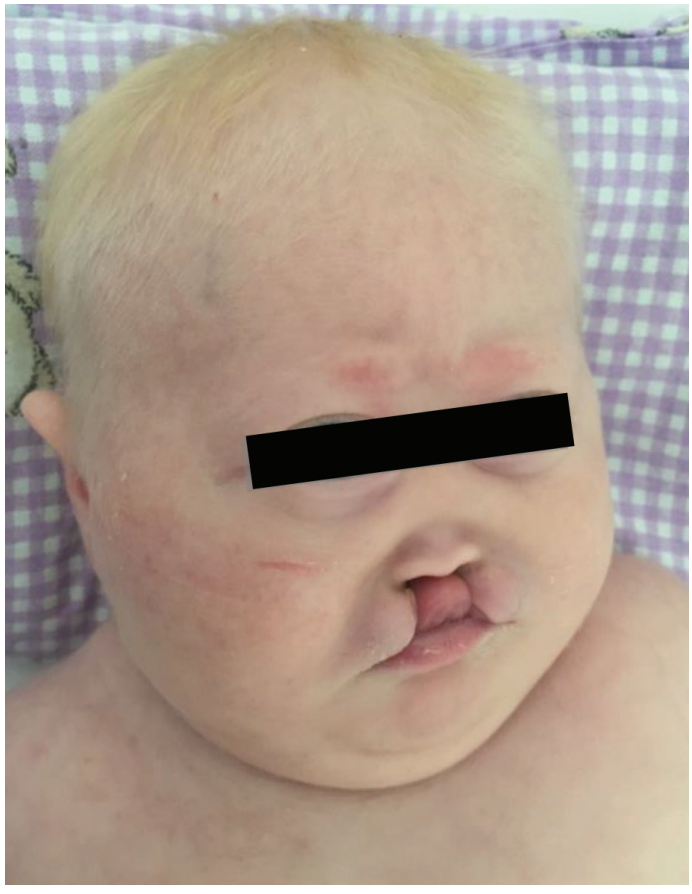

Figure 3. A case of holoprosencephaly with cleft palate/lip and anterior and posterior pituitary insufficiency (from the files of Erciyes University Faculty of Medicine, Department of Neonatology)

Physical examination findings and symptoms: Height, weight and head circumference should be measured in the newborns. Fontanelle size, eyes, cleft palate/lip, hepato-splenomegaly, lymphadenopathy, jaundice and malformations are assessed. Presence of microphallus and undescended testicles are noted in the genital examination.

Syndromes accompanied by hypophyseal deficiency are listed in Table 4 (1).

Endocrine Evaluation

Pituitary-adrenal axis: ACTH deficiency may be life threatening. Quick action is important, especially with asymptomatic midline defects. Circadian rhythm in cortisol secretion does not mature in the first six postnatal months. Thus, cortisol should be measured every hour of the day instead of only in the morning (34). Mehta et al (21) interpret cortisol values below 175 nmol/L (6.34 micrograms/dL) at 8 o'clock in the morning as deficiency. Multiple random cortisol measurements are not suitable for premature and ill infants and cortisol measurement by induced hypoglycemia is not recommended. However, cortisol measurement may be useful in addition to insulin and GH measurement in infants with hypoglycemia at presentation. Cortisol deficiency is accepted to be present if cortisol response remains below 12.67 micrograms/dL in hypoglycemic infants (35). While a standard ACTH test is easy and safe, the sensitivity is approximately 80% (10). False negative results can occur even in infants with ACTH deficiency (36). A corticotropin releasing hormone test can be performed to determine ACTH deficiency in infants. However, normative values in cases of central hypothyroidism and midline defects are not known and the test is contraindicated in ill infants (37). As the circadian rhythm matures, a cortisol value of 175 nmol/L (6.34 micrograms/dL) at 8 o'clock in the morning excludes ACTH deficiency if the cortisol level is above 540 nmol/L (19.56 microgram/dL) at the 30th minute with a low dose ACTH test. The specificity of the test was found to be 100% but the sensitivity was 69% (20).

TSH deficiency: In cases of central hypothyroidism, low or normal TSH level despite a low FT4 level is striking. Central hypothyroidism is diagnosed if the free T4 level is below 0.8 ng/dL and TSH is normal or slightly elevated (38). It should be kept in mind that severe infection, sick thyroid syndrome or dopamine infusion can cause low TSH levels in infants (39). Early diagnosis is important in central hypothyroidism cases since other hormone deficiencies may be concurrent in as high as 78% of cases (1). Hypoglycemia and neonatal

Table 2. Mutations and characteristics of genes involved in pituitary gland development

Transcription factor gene	Type of inheritance	Hormone deficiencies	MRI findings	Other findings
POU1FI (PIT-1)	AR, AD	GH, TSH, PRL	APH	-
PROP1	AR	GH, TSH, LH, FSH, PRL late ACTH deficiency	APH,	Transient AP hyperplasia
HESX1	AR, AD	IGHE, KPHE	APH, EPP	Septo-optic dysplasia Corpus callosum agenesis
LHX3	AR	GH, TSH, LH, FSH, PRL ACTH may be deficient	APH, N,	Neck rotation limited Short cervical spin Sensorineural deafness
LHX4	AD	GH, TSH, ACTH in addition to FSH, LH	APH, EPP	Cerebellar anomalies
SOX2	AD (*de novo*)	HH, GH deficiency	APH	Anophthalmia, microphtalmia, esophageal atresia, genital tract anomalies, hypothalamic hamartoma, diplegia, sensorineural deafness
SOX3	X-linked	Isolated or combined GH deficiency	APH, EPP	Mental retardation
OTX2	AD	Isolated GH or GH, TSH, PRL, FSH, LH deficiency	N, APH, EPP	Bilateral anophthalmia or severe microphthalmia
TBX19 (T-PIT)	AR	ACTH	N	Neonatal hypoglycemia
PC1	AR	HH, ACTH	N	Hypoglycemia, obesity
DAX-1	X-linked	HH, adrenal hypoplasia	N	-
GLI2	AD	Panhipopituitarism	-	Holoprosencephaly
GLI3	AD	Panhipopituitarism	-	Pallister-Hall syndrome
FGF8	AD	Hipopituitarism	-	Holoprosencephaly
FGFR1	AD	Hipopituitarism	Pituitary hypoplasia	Corpus callosum agenesis, ocular defects
IGFSF1	X-linked	TSH, GH, PRL deficiency	-	Macroorchidism
Holoprosencephaly related *SHHT*, *GIF* and *SIX3*	-	Isolated GH or combined	Pituitary stalk suture or fine stalk, small adenohypophysis and ectopic neurohypophysis	Cholestasis, single upper incisor tooth
PROKR2	AR, AD	GH, TSH, ACTH	APH, EPP	Neonatal hypoglycemia, micropenis
PITX2	AD	LH, FSH	APH	Anterior eye chamber, dental hypoplasia, craniofacial dysmorphism, protuberant umbilicus

AR: autosomal recessive, AD: autosomal dominant, GH: growth hormone, TSH: thyroid stimulating hormone, PRL: prolactin, APH: anterior pituitary hypoplasia, LH: luteinising hormone, FSH: follicle stimulating hormone, ACTH: adrenocorticotropic hormone, EPP: ectopic posterior pituitary, N: normal, MRI: magnetic resonance imaging, HH: hypogonadotropic hypogonadism

Table 3. Isolated growth hormone deficiency subtypes

Type	Gene	Heredity	Phenotype
1A	*GH1*	Autosomal recessive	Postnatal severe growth failure, very low GH level, antibody development with treatment
1B	*GH1, GHRHR*	Autosomal recessive	Milder growth insufficiency, GH is present but no antibody develops with treatment
2	*GH1*	Autosomal dominant	Growth insufficiency, hypoplastic pituitary, other hormone deficiencies may be added
3	*BTK*, *SOX3* or other genes?	X-linked	Agammaglobulinemia and mental retardation are accompanying features

GH: growth hormone

hepatitis can develop if hypothyroidism is diagnosed late and mortality is reported to approach 14% in these patients (36). The necessity of a TRH test for diagnosis is controversial (40,41).

Gonadotropin deficiency: Micropenis alone or together with undescended testicles in boys is observed in isolated HH or in multiple hypophyseal 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 start to decrease around the sixth month. High gonadotropin levels may last for 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 day 15 and six months, central hypogonadism is diagnosed (43). In female infants, central hypogonadism is diagnosed if FSH is <1.0 IU/L between day 15 and two years (44,45,46,47). HH can be diagnosed with gonadotropin releasing hormone and human chorionic gonadotropin (hCG) tests in infants (48,49). Basal FSH and LH are low in infants with HH and a blunt gonadotropin response is seen after the test (37). Attention should be paid to penile growth and testicular descent in infants tested with hCG (50).

GH deficiency: It should be kept in mind that GH level is high in the neonatal period (51,52). GH can be measured directly in the neonatal period although a decrease in the GH level and an increase in insulin-like growth factor-1 (IGF-1) and IGF binding protein-3 (IGFBP-3) levels are observed in the neonatal period, starting from birth. Kurtoğlu et al (53) reported that in term infants GH levels decreased and IGF-1 and IGFBP-3 levels showed a gradual increase (Table 5). Binder et al (54), reported GH levels in the neonatal period in children who were later detected to have GH deficiency. They concluded that in the postnatal first week, a level of 7 ng/mL reflected GH deficiency and this level showed very good sensitivity and specificity-100% and 98% respectively. The same group also observed that neonatal GH deficiency was present in cases who had multiple hormone deficiency and malformations, but that isolated GH deficiency was not detected in newborns (55). It has also been reported that random GH measurement may be useful in the first 14 days in newborns (56).

Although GH stimulation tests are not recommended in infants under 12 months old, GH levels measured in infants with hypoglycemia may yield useful clinical clues to diagnosis, though the specificity is low (57,58). A GH value of <7.7 ng/mL in infants with hypoglycemia has been suggested as a criterion of GH deficiency (35). It has been reported that a glucagon stimulation test may be used in infants younger than 12 months of age (59). 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 GH level is normally expected to be above 10 ng/mL.

PRL deficiency: PRL concentration is low in cases with *POU1F1*, *LHX3*, *OTX2* and *IGFSF-1* gene mutations and in cases of panhypopituitarism. Values below 31 ng/mL in the first 30 postnatal days and 24 ng/mL between the 30th-60th days are accepted as hypoprolactinemia (60). Breast tissue should not be palpated before taking blood and it should be confirmed that no medicine affecting PRL level has been taken. PRL levels may be low in infants given dopamine as an inotropic agent in the neonatal period (61).

Diabetes insipidus: The definition for polyuria in diabetes insipidus is a daily urine output >2 liters/m^2, which corresponds to a volume of 150 mL/kg/day in the newborn (62). The suggested criterion for polyuria of 4 mL/kg/h in

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, supraumblical raphe)
Rieger	Malformations in the anterior chamber of the eye, pretuberant umbilicus, abnormal teeth, mental retardation
Johannson-Blizzard syndrome	Microcephaly, exocrine pancreatic dysfunction, recto-urethral anomalies, hypothyroidism
Pallister-Hall syndrome	Polydactyly, imperforate anus, hypothalamic hamartoblastoma

Table 5. Weekly growth hormone, insulin-like growth factor-1 and insulin-like growth factor binding protein-3 values in the neonatal period (given as means ± standard deviation). The p value shows significant change over time

Parameter	0-7 days	8-14 days	15-21 days	22-30 days	p value
GH (ng/mL)	13.6 ± 5.68^a	9.38 ± 4.06^b	8.73 ± 3.19^c	7.91 ± 5.57^b	<0.001
IGF-1 (ng/mL)	55.4 ± 49.6^a	69.6 ± 46.6^{ab}	82.3 ± 70.0^{ab}	89.5 ± 47.6^b	0.026
IGFBP-3 (ng/mL)	2043 ± 572^a	2352 ± 777^{ac}	3002 ± 856^{bc}	3133 ± 1150^{bc}	<0.001

GH: growth hormone, IGF-1: insulin-like growth factor-1, IGFBP-3: insulin-like growth factor binding protein-3.

$^{a, b, c}$:Shared different letters represent statistically significant differences and same letters represent similarity on the same line

children corresponds to a urine volume of > 6 mL/kg/hour in the neonatal period (63). In most cases of diabetes insipidus presenting in the neonatal period, anatomical defects or autosomal dominant-recessive genetic causes are present. Central diabetes insipidus presentation is also observed in cases with septo-optic dysplasia, corpus callosum agenesis and holoprosencephaly (64). Very rarely, tumours located in the posterior hypophysis and surgical intervention for craniopharyngioma cause diabetes insipidus. Symptoms such as polyuria, polydypsia (excessive drinking of water rather than formula), weight loss, growth deficiency and persistent hypernatremia despite giving fluid and dilute urine may be striking. Plasma and urine osmolarity measurements in the early hours of the morning may help in ascertaining a diagnosis (1). Serum osmolarity < 270 mosm/kg and urine osmolarity > 600 mosm/kg draw suggest an alternative diagnosis rather than diabetes insipidus. A water deprivation test is risky in the neonatal period and can only be done in special centers (33). However, a nasal desmopressin test may be performed. On the 8th and 24th hours after the application of 0.012 mL of desmopressin (1.2 microgrammes; 1 mL = 100 microgram), observation of a decrease in serum sodium and osmolarity, an increase in urine osmolarity and a decrease in diuresis support the diagnosis (65).

Radiological examinations: In newborns, bone age is assessed with knee radiography. Epiphyseal dysgenesis should also to be investigated. Brain and hypophysis imaging should be done in infants suspected of having hypopituitarism. The degree of severity of the hypopituitarism will be proportional to the extent of the neuro-radiological abnormalities (18). Pituitary gland height neurohypophysis brightness or ectopia, an undescended posterior lobe, infundibulum morphology, absence of corpus callosum and of septum pellucidum, optic nerve and chiasma, holoprosencephaly, schizencephaly, cerebellar hypoplasia, absence of fornix and presence of Chiari malformation should be assessed with imaging (66). Lack of neurohypophysis brightness supports the diagnosis in cases of central diabetes insipidus. Data on pituitary gland height in newborns are presented in Table 6 (67,68,69,70).

Genetic studies: Genetic studies should be targeted depending on family history, physical examination and laboratory and radiological findings (13,15).

Treatment Approaches and Follow-up

Cases diagnosed with neonatal hypopituitarism should be followed-up by a multidisciplinary team. Suitable hormonal treatments, providing follow-up baring in mind that some hormone deficiencies may develop slowly, ocular and neurodevelopmental follow-up in syndromic cases, acquisition of genetic data and establishing a good relationship with the family are important during follow-up.

Treatment of central hypothyroidism 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. After starting treatment dose insufficiency is monitored by measuring free T4 and overdose by free T3 concentrations (71). It is important to know the cortisol level before thyroxine replacement. This is because cortisol clearance increases and cortisol deficiency occurs when thyroxine is given to infants with low cortisol level, especially in preterm cases (72). In cases of cortisol deficiency oral hydrocortisone should be started first and thyroid replacement should be initiated subsequently. In preterm infants, daily cortisol production is reported to be 7.28 mg/m^2/day on the fifth day and 6 mg/m^2/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/m^2/day. In case of stress, the dose should be increased two- to threefold. Diabetes insipidus may develop with hydrocortisone treatment and the infant should be observed closely (33). In infants with cholestasis at initiation of treatment oral thyroxine and hydrocortisone should be administered at high dose due to absorption deficiency and it should be kept in mind that the doses should be decreased after cholestasis resolves (74).

Testosterone injection, dihydrotestosterone gel application or recombinant human gonadotropin subcutaneous infusion treatments can be initiated between the ages of 1-6 months in boys in whom HH is diagnosed (30,75,76). Acceptable results were obtained by giving 25 mg depot testosterone intramuscularly, every three weeks over a period of three months (77).

Intranasal or peroral desmopressin should be used in cases of central diabetes insipidus. The maximum plasma

Table 6. Pituitary gland height values in the neonatal period (mm)

Researcher	Number of cases and age	Pituitary gland height in mm (mean ± standard deviation)
Kitamura et al (67)	88 (0-122 days)	3.9 ± 0.7
Dietrich et al (68)	17 (0.1-1.5 weeks)	4.12 ± 1.13
	17 (1.7-6.0 weeks)	3.94 ± 0.6
Argyropoulou et al (69)	12 (0-12 months)	3.5 ± 0.5
Sari et al (70)	14 (0-12 months)	Girls 3.81 ± 0.68
	13 (0-12 months)	Boys 3.91 ± 0.75

concentration was observed after 40-55 minutes with intranasal or oral use and the half-life is nearly 3.5 hours. Urine output starts to decrease after 1-2 hours and the effect lasts from six to 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 should also be 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 maintain fluid quantities which will prevent hyponatremia (65,80).

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

Conclusion

Neonatal period is different from other periods of life. Assessment of hypothalamus-hypophysis axis different from the other stages of life. The hormonal deficiencies particularly in this period being asymptomatic make the interpretation of pathologic conditions difficult. Therefore, efforts have been made to shed light on the diagnosis and the therapeutic approach specific to this period.

Ethic

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Selim Kurtoğlu, Nihal Hatipoğlu, Ahmet Özdemir, Data Collection and Processing: Ahmet Özdemir, Analysis and Interpretation: Nihal Hatipoğlu, Literature Research: Selim Kurtoğlu, Writing: Selim Kurtoğlu, Nihal Hatipoğlu, Ahmet Özdemir.

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