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Neonatal adrenal insufficiency: Turkish Neonatal and Pediatric Endocrinology and Diabetes Societies consensus report

Neonatal adrenal yetmezlik: Türk Neonatoloji ve Çocuk Endokrinoloji ve Diyabet Dernekleri uzlaşı raporu

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Abstract

It is difficult to make a diagnosis of adrenal insufficiency in the newborn, because the clinical findings are not specific and the normal serum cortisol level is far lower compared to children and adults. However, dehydratation, hyperpigmentation, hypoglycemia, hyponatremia, hyperkalemia and metabolic acidosis should suggest the diagnosis of adrenal insufficiency. Hypotension which does not respond to vasopressors should especially be considered a warning. If the adrenocorticotropin hormone level measured simultaneously with a low serum cortisol level is 2-fold higher than the upper normal limit of the reference range, a diagnosis of primary adrenal insufficiency is definite. Even if the serum cortisol level is normal, a diagnosis of relative adrenal insufficiency can be made with clinical findings, if the patient is under heavy stress. The serum cortisol level should be measured using the method of 'high pressure liquid chromatography' or 'LC mass spectrometry'. Adrenal steroid biosynthesis can be evaluated more specifically and sensitively with 'steroid profiling'. Rennin and aldosterone levels may be measured in addition to serum electrolytes for the diagnosis of mineralocorticoid insufficiency. Adrenocorticotropic hormone stimulation test may be used to confirm the diagnosis and elucidate the etiology. In suspicious cases, treatment can be initiated without waiting for the adrenocorticotropic hormone stimulation test. In schock which does not respond to vasopressors, intravenous hydrocortisone at a dose of 50-100 mg/m^2 or a glucocorticoid drug at an equivalent dose should be initiated. In maintanence treatment, the physiological secretion rate of hydrocortisone is 6 mg/m^2/day (15 mg/m^2/day in the newborn). The replacement dose should be adjusted with clinical follow-up and by monitoring growth rate, weight gain and blood pressure. Fludrocortisone (0,1 mg tablet) is given for mineralocorticoid treatment (2x0,5-1 tablets). A higher dose may be needed in the neonatal period and in patients with aldosterone resistance. If hyponatremia persists, oral NACl may be added to treatment. In the long-term follow-up, patients should carry an identification card and the glucocorticoid dose should be increased 3-10-fold in cases of stress.

Keywords: Adrenal insufficiency, shock, newborn

Öz

Yenidoğanda adrenal yetmezlik tanısı klinik bulguların özgül olmaması ve normal serum kortizolunun büyük çocuk ve erişkinlere göre çok düşük olması gibi nedenlerle güçtür. Bununla birlikte dehidratasyon, hiperpigmentasyon, hipoglisemi, hiponatremi, hiperkalemi ve metabolik asidoz adrenal yetmezlik tanısını düşündürmelidir. Vazopressorlara yanıt vermeyen hipotansiyon özellikle uyarıcı olmalıdır. Düşük serum kortizolu ile eş zamanlı adrenokortikotropik hormon düzeyi referans aralığının üst sınırının iki katından yüksekse primer adrenal yetmezlik tanısı kesindir. Serum kortizol düzeyi normal olsa bile, hasta ağır stres altındaysa, klinik bulgularla relatif adrenal yetmezlik tanısı konabilir. Serum kortizol düzeyi 'high pressure liquid chromatography' ya da 'LC mass spectrometry' yöntemi ile ölçülmelidir. 'Steroid profiling' ile adrenal steroid biyosentezi daha özgül ve duyarlı değerlendirilebilir. Mineralokortikoid yetersizliğinin tanısı için serum elektrolitlerinin yanısıra renin ve aldosteron düzeyi ölçülebilir. Tanının doğrulanması ve etiyolojinin aydınlatılması için adrenokortikotropik hormon uyarı testine başvurulabilir. Şüpheli olgularda adrenokortikotropik hormon uyarı testi beklenmeden tedavi başlanabilir. Vazopressorlara yanıtsız şokta İv hidrokortizon 50-100 mg/m^2 ya da eşdeğer dozda glukokortikoid başlanmalıdır. İdame tedavisinde hidrokortizonun fizyolojik sekresyon hızı 6 mg/m^2/gün; yenidoğanda 15 mg/m^2/gündür. Replasman dozu klinik izlem, büyüme hızı, kilo alımı, kan basıncı izlemi ile ayarlanmalıdır. Mineralokortikoid tedavisi için fludrokortizon (0,1 mg tablet) 2x0,5-1 tablet verilir. Yenidoğan döneminde ve aldosteron direnci olan hastalarda daha yüksek doz gerekebilir. Hiponatremi sebat ederse tedaviye ağızdan NaCl eklenebilir. Uzun süreli izlemde hastalar tanıtıcı kart taşımalı, stres durumlarında glukokortikoid dozu 3-10 misli artırılmalıdır.

Anahtar sözcükler: Adrenal yetmezlik, şok, yenidoğan

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Definition of neonatal primary adrenal insufficiency

- The most important criterion in the diagnosis of primary adrenal insufficiency is clinical findings. Hypoglycemia, hyponatremia, hyperkalemia, dehydration, metabolic acidosis, hyperpigmentation, and hypotension not responding to vasopressors are warning signs. In a patient with normal renal functions, a Na/K ratio below 20 strongly supports adrenal insufficiency (1) (⊕⊕⊕◯). Secondary adrenal insufficiency is related to adrenocorticotropic hormone (ACTH) deficiency and hyperpigmentation is not expected.
- In newborns and preterms, the diagnosis of adrenal insufficiency should be supported by clinical findings because the normal serum level of cortisol is very low (2).
- Normal cortisol level (μg/dL) (2):

  Preterm

26-28 weeks	4th day: 1-11
31-35 weeks	4th day: 2.5-9.1

  Mature

3rd day:	1.7-14
7th day:	2-11
1-11 months:	2.8-23

- If the ACTH level accompanied by low serum cortisol level is above 2-fold of the upper limit of the reference range, a definite diagnosis of primary adrenal insufficiency is made (3) (⊕⊕⊕◯).
- The rennin and aldosterone levels should also be measured to detect mineralocorticoid insufficiency (⊕⊕⊕◯).
- The diurnal rhythm of cortisol starts in 6-12 months and develops up to the age of 3 years. Therefore, the time of obtaining blood is not important in newborns; however, it is difficult to interpret a single measurement and it is beneficial to perform a few measurements (1).
- The hormone levels should be evaluated according to the clinical status of the patient. A serum cortisol level within normal limits in a patient under heavy stress does not exclude the diagnosis of adrenal insufficiency. Normal cortisol may be relatively insufficient for heavy stress. This condition is defined as relative adrenal insufficiency. The degree of stress may be specified by physician's clinical evaluation (4).

Which method should be used to measure serum cortisol level?

- Immunologic methods generally overestimate steroid metabolites because they have low specificity and the diagnosis of adrenal insufficiency may be missed with measurements performed with these methods.
- High-performance liquid chromatography triple quadrupole mass spectrometry (HPLC, LC-MS/MS) is more specific and has additional advantages including very little preliminary preparation and small sample requirement. Many steroids can be measured consecutively with the 'steroid profiling' method.
- Low levels found with HPLC may erroneously lead to a diagnosis of adrenal insufficiency because it performs measurements that are only specific for cortisol.
- HPLC and LC-MS/MS methods should be preferred and the results should be evaluated using normal ranges of the same method (5, 6).

Should adrenocorticotropic hormone stimulation tests be performed?

- A diagnosis of adrenal insufficiency can be made with basal values in the presence of clinical suspicion. However, it should be kept in mind that recurrent hypoglycemia may blunt cortisol response. In emergency situations, replacement treatment should not be postponed for the test (⊕⊕⊕◯). However, the test can be performed and treatment can be initiated without waiting for the results if the conditions and the baby's clinical status are appropriate.
- If a definite diagnosis cannot be made, the patient's status is stable and measurement of the other steroid metabolites is required for differential diagnosis, the ACTH test is performed.
- In patients in whom steroid treatment has been previously initiated, the ACTH test can be performed 48 hours after the final dose of steroid treatment. The hypothalamo-pituitary adrenal (HPA) axis generally reaches a capacity that is sufficient for giving an adequate response on the 14th day (3, 4).

If adrenocorticotropic hormone test is to be performed, which dose should be used?

- A standard dose (250 μg) or low dose (1 μg) may be used. A low dose is more sensitive in patients in whom central adrenal insufficiency is considered and in the diagnosis of subclinical (relative) adrenal insufficiency. It is preferred to evaluate HPA axis suppression in patients who receive steroid treatment (⊕⊕◯◯).
- The test can be performed at any time. In patients who receive steroids, the drug should be discontinued at least 48 hours previously (3, 4).

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What is the normal response to adrenocorticotropic hormone stimulation?

- The normal response has not been definitely described in newborns. In older children, an increase of 7 ug/dL (190 nmol/L) in cortisol response at the 60th minute compared with the basal value or a peak response of >18 ug/dL (500 nmol/L) is normal (⊕⊕◯◯). A study reporting that the lower limit of 13 ug/dL (360 nmol/L) was acceptable in newborns and preterm babies was published (7).
- Hormone levels should again be evaluated together with clinical findings (3, 4).

Neonatal hypotension and its findings

- In newborns, hypotension can be defined as a systolic, diastolic, and mean blood pressure below <95% confidence interval by gestational age and postnatal age (8-10). The clinical findings include impaired tissue perfusion, cold extremities, a capillary filling time above 3 s, weak pulse, acidosis, increased lactate (>2.8 mmol/L), and decreased urine output (<1 cc/kg h).
- In treatment, 0.9% normal saline load (10 cc/kg) is recommended if hypovolemia findings are present. In patients who do not have hypovolemia findings, the primary option is to administer dopamine 5 µg/kg/min and the dose can be incremented up to 20 µg/kg/min depending on the response. Dobutamine may be added in patients with myocardial dysfunction. In patients in whom blood pressure does not improve despite dopamine and dobutamine, hydrocortisone is given at a dose of 1 mg/kg. Blood samples should be obtained for basal cortisol measurement before administering hydrocortisone. If a response is obtained, hydrocortisone at a dose of 0.5-1 mg/kg every 6-8 hours for 2-3 days is recommended. Dexamethasone should not be used because of its central nervous system adverse effects. In patients in whom hypotension persists, adrenaline at dose of 0.05 µg/kg/min is initiated and the dose may be increased up to 0.3 µg/kg/min (11-14).
- Should hydrocortisone treatment be given in vasopressor-unresponsive shock in critically ill preterm and term babies? Should basal cortisone be measured before giving hydrocortisone? If it is to be measured, which cortisone level should be considered as adrenal insufficiency? Who should undergo adrenocorticotropic hormone tests?
- In preterms, transient adrenocortical insufficiency may be observed because of decreased capacity of cortisol synthesis due to immature hypothalamo-pituitary axis and deficiency of interim enzymes including 11b-hydroxilase. In addition, volume expander- and vasopressor-unresponsive hypotension may occur in relation to relative adrenal insufficiency under stress. Mature adrenal response against stress is observed in only 27% of preterm babies. Insufficient cortisol response is given to adrenocorticotropic hormone stimulation in the first week.
- In shock that does not respond to vasopressor, hydrocortisone may be given after obtaining a blood sample for basal cortisone without waiting for the result. Here, the dose of hydrocortisone should be 50-100 mg/m^2, which is used in adrenal crisis and continued according to clinical response (⊕⊕⊕◯).
- Serum cortisol level should be evaluated according to the degree of stress and clinical response should be considered primarily.
- An adrenocorticotropic hormone test may be performed after the patient becomes stable by interrupting steroid treatment for 48 hours with the objective of evaluating adrenal reserve (3, 4) (⊕⊕⊕⊕).

Should replacement treatment be given to patients who received antenatal steroid treatment?

- If a clinical picture of adrenal insufficiency is present in patients who received antenatal steroid treatment, adrenal suppression should be considered; treatment should be initiated knowing that this may not be a permanent condition and it should be planned to taper the dose (4).

Glucocorticoid and mineralocorticoid treatment in newborns

- The physiologic secretion rate of hydrocortisone is 6 mg/m^2/day (15 mg/m^2/day in newborns). In adrenal crisis, hydrocortisone is initiated at a dose of 50-100 mg/m^2 or equivalent glucocorticoid treatment is initiated. Treatment should be continued with a physiologic replacement dose according to clinical findings. The daily hydrocortisone dose should be divided into three or four doses (⊕⊕◯◯). If intravenous hydrocortisone is not available, equivalent prednisolone may be given, though it is not preferred. Prednisolone is being used by necessity because intravenous hydrocortisone is not available in our country.
- Treatment should be initiated with a higher dose in congenital adrenal hyperplasia (CAH) and in newborns with cholestasis. The dose is reduced in patients with cholestasis when cholestasis dissolves.

Table 1. Drug doses used in treatment of adrenal insufficiency and glucocorticoid equivalence table

Glucocorticoid (hydrocortisone)	
Maintenance	12-20 mg/m^2/day in 3 divided doses
Stress dose in hemodynamically stable patient (acute disease)	40 mg/m^2/day Po/IV/IM in 3-4 doses
Severe disease, hemodynamically unstable patient, major surgery	100 mg/m^2 IV, subsequently 25 mg/m^2 /dose every 6 hours, 24-48 hours
General anesthesia	50 mg/m^2 IV, IM, 30-60 minutes before anesthesia
Mineralocorticoid (fludrocortisone)	0.05-0.3 mg/day per oral 1-2 times daily
Salt	0.5-5 mmol/kg/day in 4-6 doses
Glucocorticoid dose equivalence table	
Steroid	mg equivalent
Hydrocortisone	20
Prednisolone	5
Prednisone	4
Dexamethasone	0.75

- Long-acting synthetic steroids, especially dexamethasone, should be avoided (⊕⊕◯◯).
- The replacement dose should be adjusted by clinical follow-up, growth rate, weight gain, and blood pressure follow-up.

For mineralocorticoid treatment, fludrocortisone is administered with a dose of 2x0.5-1 tablet (0.1 mg tablet). Higher doses may be needed in the neonatal period and in patients with aldosterone resistance. The dose should be increased according to electrolyte and blood pressure monitoring (4, 15). Simultaneous NaCl is initiated. If hyponatremia persists, NaCl replacement should be increased (15): 1 teaspoon = 5 g; 1 g salt = 17 mEq Na

Normal Na requirement: 2-4 meq/kg/day. It may be increased up to 8-10 meq/kg/day, if necessary.

Treatment of adrenal crisis

- Treatment should be initiated immediately if adrenal crisis is suspected (⊕⊕⊕◯).
- Primarily, fluid treatment is initiated; 20 mL/kg 0.9% normal saline infusion is administered in one hour; subsequently, the deficit is calculated according to sodium and fluid loss and half of the calculated fluid is given in the first eight hours such that a constant glucose infusion is also provided.
- Hydrocortisone should be immediately given by the intravenous route at a dose of 50 mg/m^2; it should be continued at a dose of 50-100 mg/m^2/day (⊕⊕⊕◯).
- If hydrocortisone is not available, equivalent prednisolone should be preferred.
- Florinef acetate at a dose of 0.1-0.2 mg should be given orally every 12-24 hours.
- One should be careful in terms of acidosis, hypoglycemia, and hyperkalemia and supportive treatment should be given.
- After the picture of adrenal crisis improves clinically and biochemically, the dose of glucocorticoid is reduced by 25-30% daily up to the physiologic replacement dose.
- If electrolyte imbalance is present, fludrocortisone should be initiated at the dose stated above (8).
- Drug doses are shown in Table 1 (16).

Prophylaxis

- Patients should carry patient an identification card; stress doses should be written on the card.
- In case of minor stress, the maintenance dose is increased 3-fold.
- In case of major stress, the maintenance dose is increased 10-fold (4) (⊕⊕◯◯).

Note: Evidence quality scoring was performed according to the publication and scale shown below.

Swiglo BA, Murad MH, Schünemann HJ, et al. A case for clarity, consistency, and helpfulness: state-of-the-art clinical practice guidelines in endocrinology using the grading of recommendations, assessment, development, and evaluation system. J Clin Endocrinol Metab 2008; 93: 666-73.

Evidence quality score:
⊕◯◯◯: very low
⊕⊕◯◯: low
⊕⊕⊕◯: moderate
⊕⊕⊕⊕: high

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