Adrenoleukodystrophy: Guidance for Adrenal Surveillance in Males Identified by Newborn Screen

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Context: Adrenoleukodystrophy (ALD) is a peroxisomal disorder associated with neurologic decompensation and adrenal insufficiency. Newborn screening for ALD has recently been implemented in five states with plans to expand to all 50 states in the United States. Adrenal insufficiency ultimately develops in most males with ALD, but the earliest age of onset is not well established.

Objective: These clinical recommendations are intended to address screening for adrenal insufficiency in boys identified to have ALD by newborn screen.

Participants: Seven members of the Pediatric Endocrine Society Drug and Therapeutics/Rare Diseases Committee, with clinical experience treating children with ALD and adrenal insufficiency, and a pediatric endocrinologist and laboratory director were selected to be on the working committee.

Consensus Process: The authors comprised the working group and performed systematic reviews of the published literature regarding adrenal insufficiency and ALD. The recommendations were reviewed and approved by the larger Pediatric Endocrine Society Drug and Therapeutics/Rare Diseases Committee and then by the Pediatric Endocrine Society Board of Directors.

Conclusions: There is limited literature evidence regarding monitoring of evolving adrenal insufficiency in male infants and children with ALD. The recommendations suggest initiating assessment of adrenal function at diagnosis with ALD and regular monitoring to identify boys with adrenal insufficiency in a timely manner and prevent life-threatening adrenal crisis. These recommendations are intended to serve as an initial guide, with the understanding that additional experience will inform future guidelines. (***J Clin Endocrinol Metab*** **103: 4324–4331, 2018)**

Adrenoleukodystrophy (ALD) is a peroxisomal disorder characterized by impaired transport of very-long-chain fatty acids (VLCFAs) into peroxisomes, preventing normal VLCFA breakdown and causing VLCFA accumulation in multiple tissues. ALD has a variable phenotypic presentation, affecting adrenal

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Abbreviations: 3β-HSD, 3β-hydroxysteroid dehydrogenase; ALD, adrenoleukodystrophy; AMN, adrenomyeloneuropathy; NYS, New York state; VLCFA, very-long-chain fatty acid.

function, central and peripheral nervous systems, and testicular function. There are six phenotypic presentations of ALD in males: (1) childhood cerebral ALD, (2) adolescent cerebral ALD, (3) adult cerebral ALD, (4) adrenomyeloneuropathy (AMN), (5) adrenal insufficiency only (also referred to in literature as "Addison only"), and (6) asymptomatic. Childhood cerebral ALD, which presents as a progressive neurodecompensation (typically starting with behavioral changes followed by decline to gait abnormalities, decline in school performance, dementia, deafness, cortical blindness, seizures, and hemi/quadriparesis over a 6-month to 2-year period), is the most devastating and is noted at a frequency of 31% to 35% in males with *ABCD1* mutations. Childhood cerebral ALD is most common between 4 and 8 years of age and rarely presents prior to 3 years of age; the prevalence of adrenal insufficiency in this group of boys is reported to be 79% to 90%. The adolescent and adult forms of cerebral ALD have a similar neurologic presentation and are reported at frequencies of 4% to 7% and 2% to 3%, respectively, among males with *ABCD1* mutations. AMN, which has a reported frequency of 40% to 46%, tends to present in the third and fourth decades of life as a progressive spastic paraparesis, often with bladder and bowel incontinence, ataxia, impotence, and mood disorders noted. The prevalence of adrenal insufficiency is reported to be roughly 70% at time of presentation with AMN and increases with age. Adrenal insufficiency, only, is reported to be relatively high during childhood (~50%) and declines with age, as neurologic complications of ALD develop. The peak onset of adrenal insufficiency is thought to be during childhood between 3 and 10 years, but long-term monitoring data for adrenal insufficiency are lacking. Asymptomatic patients are common during childhood, but thought ultimately to account for <5% of all adult males with *ABCD1* mutations (1–4). Hematopoietic stem cell transplant has been established as a therapeutic intervention to stabilize neurologic deterioration and increase survival when performed in the earliest stages of the cerebral disease (5). As early diagnosis and intervention can be lifesaving, ALD recently has been identified as a condition for newborn screening. New York state (NYS) was first to initiate screening on 30 December 2013 following passage of Aidan's law (6). Newborn screening has since been implemented in four additional states (Connecticut, California, Minnesota, and Pennsylvania), with plans to expand to all states based on the addition of ALD to the Recommended Universal Screening Panel in 2016. Although much of the literature and screening guidelines have focused on neurologic symptoms associated with childhood cerebral ALD, identification of affected patients by newborn screening also provides the opportunity to address the associated adrenal insufficiency. Adrenal insufficiency occurs in the majority of those with cerebral ALD but also occurs in those with AMN and can be found in isolation in males with ALD. Adrenal insufficiency is often an unrecognized condition with subtle symptoms, and early detection and treatment can prevent life-threatening adrenal crisis (7). Unlike congenital adrenal hyperplasia, another condition on the Recommended Universal Screening Panel that is known to be associated with adrenal insufficiency from birth, adrenal insufficiency associated with ALD develops over time in males. Females do not typically develop adrenal insufficiency but are at risk for neurologic symptoms later, in adult life. There are gaps in our current understanding of when and how quickly adrenal insufficiency associated with ALD will present. These recommendations are intended to provide an initial uniform protocol to help manage patients identified in the newborn period with ALD.

Epidemiology and Pathophysiology

ALD has been described in all ethnic groups. Prior to the advent of newborn screening, the reported incidence was 1:14,000 female births and 1:21,000 male births, but it has been hypothesized the discrepancy in sex incidence may be in part due to mortality secondary to underdiagnosis of boys with primary adrenal insufficiency (1, 8). Personal communication with NYS newborn screening officers as of 31 May 2017 indicates 52 newborns have screened positive for ALD out of ~800,000 screened. Of these, 26 were affected males, 25 were female heterozygotes, and 1 was a male with Klinefelter syndrome. This is an incidence of ~1:15,400 births with no marked difference in males and females. In the most recent reported year of 2016, there were 3.95 million births in the United States (9). Given the reported rates of positive ALD screens in NYS, an estimated 256 infants would be identified yearly with ALD in the United States. Although the reported sensitivity for newborn screening detecting ALD in boys is high, the true false-negative rates may not be known for years, as symptoms of ALD may not develop for decades (10). It is also important to note the detection rate of female heterozygotes may be low, as ~15% to 20% have normal VLCFA concentrations, which is the first and second level of the newborn screening protocol for ALD in NYS (11). The prevalence of adrenal insufficiency is reported to be 86% in males with ALD, and the earliest reported asymptomatic patient with adrenal insufficiency was 5 months old (12). The authors have anecdotal experience of male infants with ALD demonstrating biochemical evidence of adrenal insufficiency as young as

3 months of age. Fewer than 1% of female heterozygotes are reported to develop adrenal insufficiency, and neurologic symptoms are not reported during childhood. However, by 60 years of age, >80% of women with ALD-causing mutations exhibit signs or symptoms of neurologic dysfunction, with myelopathy and peripheral neuropathy being the most common manifestations (13).

ALD is caused by mutations in the *ABCD1* gene (Online Mendelian Inheritance in Man #300100), located at the Xq28 locus. More than 750 disease-causing mutations in *ABCD1* have been identified (adrenoleukodystrophy.info/), and there is no known genotype-phenotype correlation (14–16).

ALD protein, the product of *ABCD1*, is an ATP-binding cassette protein transporter located in the peroxisomal membrane and hypothesized to be responsible for the transport of VLCFAs across the membrane. Defects in ALD protein are thought to lead to an inability to properly transport VLCFAs across the peroxisome membrane and lead to elevations in the plasma VLCFA [hexacosanoic acid (C26:0) and lignoceric acid (C24:0)] (16–18). The VLCFAs accumulate in the zona fasciculata and zona reticularis of the adrenal cortex, are cytotoxic to the adrenocortical cells, and lead to impaired production of cortisol and androgens, respectively. Classically, on histopathology, the adrenocortical cells appear striated with cytoplasmic lamellae and decreased rough endoplasmic reticulum (19). *Ex vivo* studies have also demonstrated VLCFAs alter the microviscocity of the cortical cell lipid membrane and are associated with decreased ACTH-stimulated production of cortisol, consistent with VLCFAs interfering with ACTH receptor function (20). Mineralocorticoid deficiency, leading to salt wasting, is not typically described in boys with ALD, consistent with the preservation of aldosterone production and the lack of VLCFA accumulation in the zona glomerulosa of the adrenal cortex (16, 21, 22). The mechanisms for the development of cerebral ALD and AMN are beyond the scope of discussion for these recommendations. The neurologic symptoms likely develop not only because of VLCFA accumulation in neurons, but also as a result of a combination of VLCFA induction of oxidative stress and apoptosis (23, 24). The degree to which VLCFAs are elevated is not predictive of the type of ALD that will develop. Furthermore, there is no known correlation of the degree of VLCFA elevation with the onset of adrenal insufficiency (25). Hematopoietic stem cell transplant does not prevent the progression of adrenal insufficiency as it does cerebral disease. It is unknown whether gene therapy, also used to treat cerebral ALD, will influence the development of adrenal insufficiency (26). As noted above, pathophysiology of adrenal disease is related to the accumulation of the VLCFAs in the adrenal cortex that has already reached a degree that is irreversible by the time of transplant, whereas cerebral ALD has a considerable progressive inflammatory component that is stabilized by the transplant (27).

Physiology of Cortisol and Aldosterone From Birth to Age 3 Years

The interpretation of screening tests for adrenal insufficiency in pediatrics requires an understanding of changes in adrenal physiology from fetal life to early childhood. The fetal adrenal consists mainly of a "fetal zone" that has limited expression of 3β-hydroxysteroid dehydrogenase (3β-HSD), which is necessary for synthesizing cortisol and aldosterone. The fetal zone thus secretes primarily dehydroepiandrosterone and dehydroepiandrosterone sulfate (28–30). The remaining 10% to 20% of the fetal adrenal is composed of a "transitional zone" and a "definitive zone," both of which express 17α-hydroxylase and 3β-HSDII and thus have the capacity to synthesize cortisol. Near term, the fetal adrenal produces cortisol at a rate per unit body weight similar to that in adults (28). Following delivery, the fetal zone begins to involute, losing ~50% of its mass within the first month, and the definitive zone begins to differentiate into the inner, glucocorticoid-producing, zona fasciculata and outer, mineralocorticoid-producing, zona glomerulosa (29, 30). The zona reticularis is not evident until later in childhood (30).

Changes in the structure of the adrenal gland are accompanied by substantial changes in adrenal steroid levels during birth and infancy. Three principles regarding cortisol production are important. First, basal cortisol levels are generally lower in infancy than in childhood. Following delivery, cortisol and ACTH peak ~2 hours of postnatal life. ACTH then rapidly declines to normal childhood levels. Cortisol decreases further, however, and remains lower during infancy than compared with later childhood and adulthood (31–33). Cortisol levels in premature infants are similar to those in term infants during the first week of life, but levels of steroidogenic precursors are often higher, suggesting immaturity of 3β-HSD and 11β-hydroxylase activity (34). Second, cortisol-binding globulin is low in neonates, such that low total serum cortisol levels may not necessarily reflect low bioactive cortisol (35, 36). Third, cortisol secretion is pulsatile in infants, as in adults, but diurnal rhythms of ACTH and cortisol are not present at birth. Reports vary significantly regarding the age at which circadian rhythms are established. Although there is general consensus that the circadian rhythm begins to develop within the first 1 to 6 months of life, some studies

suggest that it may not be fully established until 3 years of age (37). Given the changing patterns of secretion, varying ages at which the diurnal secretory patterns of ACTH and cortisol are established, and potential changes in cortisol-binding globulin, it is not surprising considerable interinfant variability in nonstimulated total cortisol levels exist during infancy (33). Thus, basal serum cortisol levels during the first year of life have limited diagnostic utility, whereas they may be more useful after 1 year of age.

Normal Cutoffs for ACTH and Cortisol at Baseline and After Cosyntropin Stimulation

The Endocrine Society's Clinical Practice Guideline "The Diagnosis and Treatment of Primary Adrenal Insufficiency" recommends standard (*i.e.*, high-dose, 250 μg for children ≥2 years of age, 15 μg/kg for infants, and 125 μg for children <2 years of age) cosyntropin stimulation testing to establish the diagnosis of primary adrenal insufficiency, with a peak cortisol level <18 μg/dL (to convert mg/dL to nmoles/L, multiply by 27.588) indicating adrenal insufficiency. If stimulation testing is not feasible, the recommendation is to obtain morning cortisol and ACTH levels. A cortisol <5 μg/dL with a plasma ACTH more than two times the upper limit of normal makes primary adrenal insufficiency highly likely (38). Elevation of ACTH with normal cortisol may represent the earliest stage of adrenal insufficiency. The Pediatric Endocrine Society in 2006 suggested that an ACTH >100 pg/mL (to covert pg/mL to pmol/L, multiply by 0.2222) and cortisol <10 μg/dL are suggestive of primary adrenal insufficiency and should be followed by cosyntropin testing if the diagnosis is uncertain (7).

Normal ranges for baseline and stimulated cortisol are assay dependent and variable. Immunoassays may use different detection antibodies and result in higher concentrations than HPLC (39). There are limited data regarding baseline and stimulated cortisol and ACTH concentrations in healthy infants and young children. Table 1 summarizes selected published studies reporting normal serum cortisol levels during childhood (39–42). Studies are limited by size and lack of uniform assay for cortisol measurement. Several studies have also used salivary cortisol assays to assess morning values and circadian rhythm in early childhood. These methods are still only used in clinical research settings (33, 43).

There are no established ACTH reference ranges in infancy, and only one study of 30 healthy, full-term 4-day-old to 7-day-old infants reported a mean ACTH of 50.2 ± 6.9 pg/mL (42). In addition to having limited reference data, another limitation to ACTH interpretation is the potential for unreliable test results. Because ACTH is prone to proteolytic degradation, standard immunochemiluminometric assays tend to report lower than expected values because of errors in specimen handling. Under ideal conditions, ACTH is collected in an EDTA tube, immediately stored on ice, plasma is separated in a cooled centrifuge, and analysis occurs within 1 hour or the sample is stored at −80°C (44, 45). Given the potential pitfalls with the ACTH assay, the clinician should be cautious interpreting any single result. If suspicion is high for adrenal insufficiency, one should consider pursuing additional testing, particularly if there are concerns for mishandling of the ACTH specimen prior to analysis.

Suggested Best Clinical Practice

The authors comprised the working group for ALD within the Pediatric Endocrine Society Drug and Therapeutics/Rare Diseases Committee. The authors independently performed literature reviews to summarize the known physiology of the hypothalamic-pituitary-adrenal axis during infancy and to summarize the known pathophysiology of ALD. Only one cohort study, with 49 patients, was found to evaluate for adrenal insufficiency in asymptomatic patients with ALD, and there were limitations to the definition of adrenal insufficiency, based on the lack of ACTH reference ranges under the age of 3 years (12). The other reports of adrenal insufficiency in ALD were case studies or series. Given the limited literature regarding adrenal insufficiency in ALD, systematic grading for quality of the literature was not performed. The recommendations presented were based on the summary of the limited literature, the authors' clinical experience, and communications with those treating infants with ALD and previously graded clinical guidelines for primary adrenal insufficiency (7, 38). After coming to consensus within the working group, recommendations were distributed to the entire Drug and Therapeutics/Rare Diseases Committee of the Pediatric Endocrine Society to ensure consensus among that committee. Subsequently, the recommendations were also approved by the Board of Directors of the Pediatric Endocrine Society. The algorithm in Fig. 1 is presented as the expert consensus recommendation for best clinical practice testing and treatment of infants identified on newborn screening as having ALD.

Due to concerns for potential early, unrecognized adrenal insufficiency and anecdotal experience of male infants as young as 3 months old with biochemical evidence of adrenal insufficiency, the consensus of the group is to start the endocrine evaluation shortly after confirmation of

Table 1. Summary of Select Studies of Normal Cutoffs for Cortisol at Baseline and After Cosyntropin Stimulation

Publication	Cortisol Assay Methodology	Patients	Baseline Cortisol	Cortisol After Cosyntropin
Chrousos *et al.* (39)	HPLC	Pretreatment for asthma (n = 118)		High dose (125 μg)
		5 to <9 mo	6.15 (2–24.4) μg/dL (5 to <9 mo)	23 (5.9–36.7) μg/dL (5 to <9)
		9 to <12 mo	9.2 (2–23.9) μg/dL (9 to <12 mo)	24.2 (7–38.3) μg/dL (9 to <12)
		Pretreatment for allergic rhinitis (n = 68)		Low dose (10 μg)
		2 to <3 y	8.6 (4.4–17.4) μg/dL (2 to <3 y)	24.6 (21–31.9) μg/dL (2 to <3 y)
Elmlinger *et al.* (40)	Automated Chemiluminescence Assay System (Immulite®; Siemens)	16 d to 3 y Males (n = 42) Females (n = 44)	2.5 percentile 4 μg/dL (males) 5.6 μg/dL (females)	N/A
Eyal *et al.* (41)	Electrochemiluminesence	Referred for testing to rule out adrenal pathology (patients with pathology excluded) 7 mo to 17.7 y (n = 85)	11.53 ± 5.74 μg/dL 3rd percentile: 3.5 μg/dL 97th percentile: 25.6 μg/dL	High dose (250 $\mu g/m^2$; maximum 250 μg) 32.95 ± 6.22 μg/dL 3rd percentile: 24.3 μg/dL 97th percentile: 44.4 μg/dL
Soliman *et al.* (42)	Solid-phase radioactive immunoassay	4–7-d healthy newborns (n = 30)	14.8 ± 1.9 μg/dL	Low dose (1 μg/1.73 m^2) 38.1 ± 5 μg/dL High dose (250 μg/1.73 m^2) 84 ± 6.9 μg/dL

Cortisol values for the study by Chrousos *et al.* (39) are expressed as mean with 95% CIs. For the studies by Eyal *et al.* (41) and Soliman *et al.* (42), the cortisol values are expressed as mean ± SD unless noted otherwise.

Abbreviation: N/A, not applicable.

the ALD diagnosis. As adrenal insufficiency symptoms are challenging to identify, particularly in children under the age of 2 years, the group also agrees reassessment every 3 to 4 months is an appropriate time frame to detect biochemical adrenal insufficiency prior to the development of frank symptoms. As noted above, because predictable diurnal secretion of ACTH and cortisol starts to develop between 1 and 6 months of age and can take up to 3 years to be established, samples in young infants may be obtained at random, prior to establishment of the diurnal secretion of ACTH and cortisol. By 6 months to 1 year of age and beyond, samples should be collected close to 8 AM. The most recent Endocrine Society and Pediatric Endocrine Society clinical practice recommendations for evaluation of adrenal insufficiency are used as guides for establishing cutoff values for ACTH and cortisol (7, 38). Although there are no clear normal reference ranges for ACTH under the age of 3 years, the group agrees an ACTH value >100 pg/mL and cortisol <10 μg/dL is suggestive of adrenal insufficiency (7). Children with normal ACTH and cortisol levels (<100 pg/mL and ≥5 μg/dL, respectively) do not require immediate treatment and should be retested in 3 to 4 months. ACTH values of ≥300 pg/mL are thought to be associated with maximal stimulation of the adrenal gland, and cortisol should be interpreted as though an ACTH (cosyntropin) stimulation test has been performed (46). Children with clearly abnormal ACTH and cortisol levels (>300 pg/mL and <18 μg/dL, respectively) should begin daily and stress-dose glucocorticoid replacement. In the unusual event of both markedly elevated ACTH of ≥300 pg/mL and normal cortisol of ≥18 μg/dL, the recommendation is to consider repeat testing, as the ACTH is likely a reflection of abnormal adrenal function, but confirmation of abnormal ACTH value should be considered prior to commitment to chronic glucocorticoid replacement. An ACTH 100 to 299 pg/mL and a cortisol <10 μg/dL are indeterminate and should prompt high-dose ACTH (cosyntropin) stimulation testing. Unanimous consensus has not been reached on the next step in management for children with ACTH <100 pg/mL and cortisol <5 μg/dL or ACTH 100 to 299 pg/mL and cortisol ≥10 μg/dL; some recommend stimulation testing in this circumstance, whereas others recommend monitoring and repeat ACTH and cortisol as clinically indicated. Thus, we recommend clinicians consider stimulation testing or close clinical follow-up for infants and children in these categories. Given the difficulty of identifying signs and symptoms of adrenal

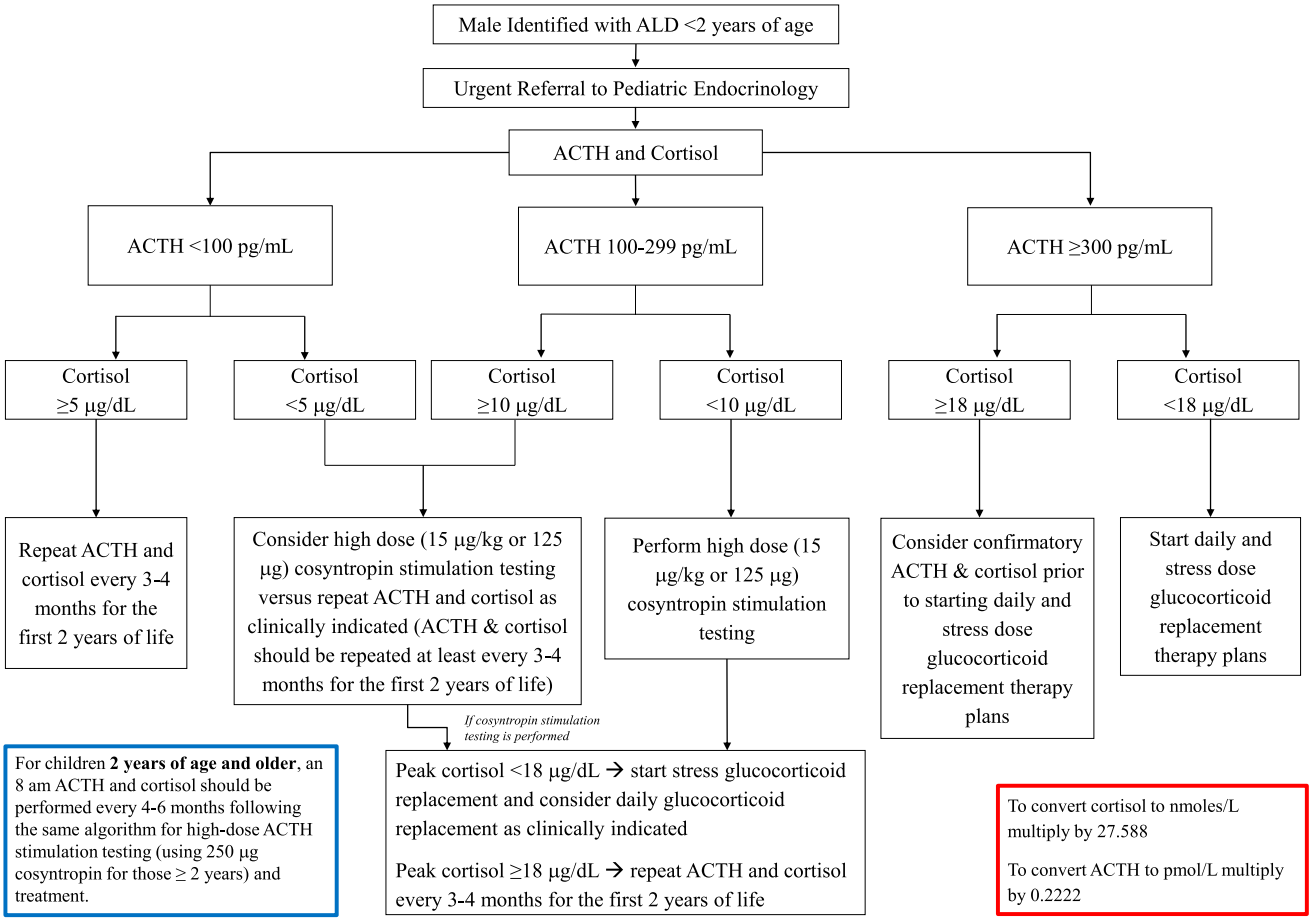

Figure 1. Suggested algorithm for surveillance of adrenal function. Due to lack of predictable diurnal variation of ACTH and cortisol, prior to 1 y of age, stimulation testing may be considered in place of baseline laboratory tests if additional follow-up will be difficult for the patient.

insufficiency in this age group, the recommendation is to monitor ACTH and cortisol every 3 to 4 months under the age of 2 years.

Because diurnal variation may not be established in early infancy before 1 year of age, timing of baseline cortisol and ACTH may not be as important compared with later childhood. ACTH should be drawn, placed on ice, and centrifuged, and then separated plasma should either be frozen or immediately processed for most accurate results. If there is clinical concern for adrenal insufficiency, high-dose cosyntropin stimulation (15 µg/kg or 125 µg cosyntropin) testing should be performed without delay. Stimulation testing should also be considered in place of baseline laboratory tests if additional follow-up will be difficult for the patient. If intravenous access is not possible, cosyntropin can be intramuscularly administered and cortisol concentrations measured from blood obtained by heel stick. Samples for cortisol measurement should be drawn prior to and 60 minutes after injection of cosyntropin and ACTH only measured prior to injection. It is also highly recommended that an assessment of adrenal function be performed before the first sedated MRI (current NYS guidelines suggest starting MRI at 6 months, but clinical practice may vary) (6). If a patient has an ACTH >300 pg/mL but passes high-dose cosyntropin stimulation testing (peak cortisol ≥18 µg/dL), hydrocortisone should be prescribed for episodes of physiologic stress, such as febrile illness, vomiting, and surgical procedures, and counseling given in regards to oral and intramuscular administration of hydrocortisone, as this may represent an early stage of evolving adrenal insufficiency.

Although rare, there are reports of mineralocorticoid deficiency in patients with ALD (25). Once the diagnosis of glucocorticoid deficiency has been made, further evaluation of aldosterone production should be considered if the patient has symptoms, such as salt craving and polyuria. Because symptoms are difficult to assess in infancy, it is recommended that serum plasma renin activity and electrolytes be drawn every 6 months. Fludrocortisone should be started when there is evidence of mineralocorticoid deficiency. Infants would also require additional salt supplementation.

The females identified by newborn screening to have elevations in VLCFAs and confirmed to be heterozygous for an *ABCD1* mutation have a very low risk for adrenal

insufficiency and cerebral ALD. Therefore, routine monitoring for adrenal insufficiency and MRI of the brain are not recommended.

As this best clinical practice guidance is based on scant clinical data, these recommendations are not meant to replace good clinical judgment as to when to begin glucocorticoid and mineralocorticoid replacement.

Conclusion

Newborn screening for ALD has the potential to identify boys with adrenal insufficiency in a timely manner to treat and prevent life-threatening adrenal crisis. Further experience with monitoring infants found to have positive screens will inform future clinical guideline recommendations.

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