Neonatal Screening for Congenital Adrenal Hyperplasia: 17-Hydroxyprogesterone Levels and CYP21 Genotypes in Preterm Infants

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ABSTRACT. Objective. Neonatal screening for congenital adrenal hyperplasia (CAH) among preterm infants is complicated by the fact that healthy preterm infants have higher levels of 17-hydroxyprogesterone (17-OHP) than term infants, resulting in a higher false-positive rate. Even when gestational age–related cutoff levels after ether extraction were used, the false-positive cases primarily comprised preterm infants. The aim of the study was to optimize the procedure for neonatal screening for CAH in preterm infants.

Methods. The 17-OHP levels in 6200 preterm infants were correlated to the gestational age. We also calculated the number of recalls for different putative cutoff levels of the 17-OHP by direct assay and after extraction in 1275 preterm infants who represented the most elevated cases in a population of approximately 30 000 preterm infants. The CYP21 genotypes and screening levels were determined in the 12 preterm infants with CAH diagnosed since the start of screening. The effect of possible interfering factors such as gestational age, neonatal stress, and prenatal glucocorticoid treatment for pulmonary maturaion was studied.

Results. The extraction procedure did not significantly improve the sensitivity or specificity of the screening, whereas it delayed the day of recall from 8 to 13 days (median). We could not demonstrate any systematic influence of the studied stress factors or the prenatal glucocorticoid treatment on the 17-OHP screening levels. In the patients with CAH, the 17-OHP levels correlated better with disease severity than with the degree of prematurity.

Conclusions. On the basis of these results, we omitted the extraction step and changed the cutoff levels in the Swedish screening program for preterm infants. We chose to use a cutoff level of 400 nmol/L plasma in infants who were born before week 35 and 150 nmol/L for infants who were born in weeks 35 and 36. For detecting more patients, the cutoff level would have to be much lower, which would result in a number of false-positive tests that we consider to be unacceptably high. It is clear that neonatal screening cannot detect all infants with CAH. Some milder forms of the disease, just like in the past, will have to be diagnosed on the basis of clinical signs and symptoms. Pediatrics 2001;108(4). URL: http://www.pediatrics.org/cgi/content/full/108/4/e68; congenital adrenal hyperplasia, 21-hydroxylase deficiency, neonatal screening, 17-OHP, preterm, CYP21.

ABBREVIATIONS. CAH, congenital adrenal hyperplasia; SW, salt wasting; SV, simple virilizing; 17-OHP, 17-hydroxyprogesterone.

Congenital adrenal hyperplasia (CAH) is a recessively inherited disorder caused by a deficiency in 1 of the enzymes necessary for the synthesis of cortisol in the adrenal cortex. More than 90% of all cases of CAH are caused by 21-hydroxylase deficiency.¹ This enzyme deficiency results in a reduced ability to synthesize cortisol and aldosterone and an increased secretion of androgens.

There is a wide spectrum of severity of CAH.¹,² Historically, the patients have been classified according to their salt-losing tendency. The most severe forms lead to a salt-wasting (SW) crisis, usually during the first weeks of life, as a result of a severe lack of both glucocorticoids and mineralocorticoids. The elevated androgen levels during embryogenesis cause virilization of the external genitalia in girls with CAH: clitoromegaly, fusion of the labia majora, and a common urethral and vaginal opening. A less severe form of 21-hydroxylase deficiency, with prenatal virilization but without life-threatening salt loss, usually is referred to as the simple virilizing (SV) form of CAH. The virilization can lead to uncertainty or even the wrong gender assignment in the neonatal period. Patients with milder forms of the disease, often referred to as nonclassic CAH, do not show signs of prenatal virilization at birth but develop symptoms of excess androgen production later in life. These patients may present with precocious pseudopuberty or growth acceleration in childhood and, as a result of accelerated bone maturation, reduced final height.

The molecular genetics of CAH attributable to 21-hydroxylase deficiency has been studied extensively. Deletion of the 21-hydroxylase gene (CYP21) and 9 smaller, pseudogene-derived sequence aberrations are responsible for approximately 95% of all affected Scandinavian CYP21 alleles³ and for the majority of CAH patients in other ethnic groups.³⁻⁷ With few exceptions, there is a clear relationship between clinical disease severity and the underlying CYP21 mutations.³⁻⁷⁻⁹ Patients with mutations that completely inactivate the gene, referred to as null mutations, have the most severe form of CAH. The I2 splice mutation is slightly less severe. The I172N mutation

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is associated with the SV phenotype. V281L is the most common mutation associated with mild, late-onset symptoms.

An elevated blood level of 17-hydroxyprogesterone (17-OHP) is used as an indicator of CAH. The technique of analyzing 17-OHP in filter-paper blood samples, using a radioimmunoassay procedure, was developed by Pang et al in 1977. Since then, nationwide and regional screening programs for CAH have been introduced in several countries. In Sweden, nationwide neonatal screening for CAH was started in 1986. Approximately 1.5 million Swedish children had been screened by the end of 1999. The prevalence of CAH in the Swedish population was 1/9800, and 80% of the patients had the SW form of the disease. Compared with the situation before screening, we were able to show several benefits of neonatal screening for CAH. Earlier diagnosis and treatment of CAH prevents the adrenal crisis and early infant death. Screening also makes an earlier correct gender assignment possible.

Healthy preterm infants often have higher plasma levels of 17-OHP than do full-term infants in the neonatal period, which results in a relatively high false-positive rate among them. The reasons for this are not fully understood, but it is attributable to a partly immaturity adrenal function with a lower 11-hydroxylase capacity as well as higher 17-OHP levels as a result of immaturity might be another important factor. Preterm infants also may have higher levels of glucuronic acid and sulfate conjugated steroid metabolites in the circulation. Poorer kidney function as a result of immaturity might be another important factor. Preterm infants also may also have higher levels of adrenocorticotropic hormone as a result of stress. To reduce the false-positive rate, gestational age or birth weight–related recall levels have been used as well as extraction procedures to minimize interference of metabolites in the assay. Even when gestational age–related cutoff levels after ether extraction were used in the Swedish screening program, the false-positive cases primarily comprised preterm infants (43%), although the preterm infants represented only 6% to 7% of the newborn population. The predictive value of positive tests for preterm infants was 3%, whereas it was 27% for full-term infants.

In addition, the situation has become even more complex. Prenatal treatment with glucocorticoids frequently is used to induce pulmonary maturation in pregnancies with an expected preterm delivery. Several authors reported basal cortisol levels in neonates to be depressed within 6 hours of treatment with dexamethasone or betamethasone and to remain low for 7 days. Some studies indicate that extremely preterm and severely ill infants have surprisingly low basal cortisol. The reasons for this have been suggested to be reduced ability to respond adequately to stress, because of either an inability to produce cortisol or an inability to recognize the stress and/or an inappropriate corticotropin-releasing hormone release. To investigate whether CAH screening can be optimized for preterm infants, we studied 17-OHP levels from direct analysis in 6200 infants who were born before gestational week 37. We also compared 17-OHP levels in direct analysis and after ether extraction in 1275 preterm infants. The effect of possible interfering factors, such as gestational age, mode of delivery, maternal treatment with glucocorticoid for surfactant induction, or asphyxia, on the screening results was studied in a group of infants who were not affected by CAH. In addition, we determined CYP21 genotypes and screening 17-OHP levels for all patients who had CAH and were born preterm in Sweden since the initiation of the screening program.

### METHODS

#### Neonatal Screening for CAH

Filter-paper blood spots collected on day 3, 4, or 5 after birth were used. 17-OHP was analyzed using fluororimmunoassay (Delphia; Perkin Elmer Life Sciences, Turku, Finland) or, before 1991, radioimmunoassay. The cutoff limit in the Swedish neonatal screening program for a positive test in term infants has been 75 nmol/L plasma since 1991 (assuming a hematocrit of 50%). For infants who were born before the 37th week of gestation, all samples with an initial 17-OHP of ≥150 nmol/L in the direct assay were reanalyzed after ether extraction. A recall level of 200 nmol/L after ether extraction was used. This is a time-consuming procedure. The analysis itself takes 1 extra day and in our laboratory was performed once or twice a week. To shorten the recall times for preterm infants with very high levels of 17-OHP, we used additional cutoff levels. The clinician in charge was contacted by telephone immediately when the result of the direct measurement of 17-OHP was above 400 nmol/L for infants who were born in gestational weeks 33 to 36 or above 600 nmol/L for infants who were born before week 33. A second filter-paper sample was requested for all infants who had a positive screening test. The second sample usually was analyzed approximately 1 week after the first screening sample. Children in whom the second sample was normalized or in whom a subsequent clinical examination failed to detect any signs of CAH were defined as false-positive cases.

#### CYP21 Genotyping

CYP21 mutation analysis was conducted using allele-specific polymerase chain reaction from genomic DNA prepared from venous blood samples. This detects the 95% of alleles that carry any of the common pseudogene-derived mutations. All additional rare alleles were characterized by direct DNA sequencing.

#### Children Included in the Study

The screening values after direct measurements of 17-OHP were collected for 6200 preterm infants who were born during 5 different periods during 1995 to 1999 (a total of 11 months). The 17-OHP level was correlated to gestational age. In the vast majority of pregnancies in Sweden, gestational age is determined by ultrasound during gestational weeks 16 to 18, which makes gestational age a reliable parameter.

For the 1275 infants who were screened between 1995 and 1999 and had an initial direct screening 17-OHP value of ≥150 nmol/L, the direct values were compared with the values after ether extraction. These infants represent a total population of approximately 30,000 screened preterm infants. We calculated the number of recalled cases that would result from different putative cutoff levels, comparing both the direct and the extraction procedures.

All preterm infants with CAH diagnosed in Sweden since the start of the screening program were identified. Their 17-OHP screening values were recorded, and the CYP21 mutations were determined. Disease severity was assessed using both CYP21 genotypes and clinical data, when possible. The number of missed and detected patients for different cutoff levels was calculated.

The screening values of 17-OHP for 88 preterm infants who were born in or before gestational week 32 (the period when prenatal glucocorticoid treatment is used) were analyzed with respect to possible interfering factors. A possible influence of prenatal glucocorticoid treatment, perinatal stress (Apagar score ≤7 at 5 minutes), and the mode of delivery was studied.

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from the last glucocorticoid dose to the day of sampling was recorded.

RESULTS

The screening sample was collected on the fourth day of life (median) for the preterm as well as the full-term infants, although it was more common for the samples of the preterm infants to be collected at a later time (range: 3–16). Recall was on day 13 (median; range: 6–29) for the preterm infants, whereas it was on the eighth day of life (median) for full-term infants. The delay was attributable to the extra time required for the extraction procedure per se and the fact that it was performed once or twice per week.

The screening 17-OHP levels obtained from direct analysis of the 6200 preterm infants of different gestational ages are shown in Fig 1. The spread in 17-OHP levels was very large, especially in the most preterm infants. In 205 (3.3%) of these infants, the initial screening value was ≥150 nmol/L.

The 17-OHP levels of the 1275 preterm infants who were screened during 1995 to 1999 and had an initial 17-OHP of ≥150 nmol/L are shown in Fig 2A (direct levels) and B (levels after extraction). There is a more distinct difference between false- and true-positive tests when the ether extraction procedure is used. The numbers of recalls that would result from different putative cutoff levels are presented in Table 1.

We compared the positive predictive values for the different cutoff levels used in the direct analysis and the extraction procedure. With the currently used cutoff level of 200 nmol/L after extraction, 3 patients were missed in the screening. It is likely that a fourth patient, who had a direct value of 295 nmol/L and for whom no value after extraction was available, would have been missed, too. The predictive value of a positive test was 8%. Using the additional direct cutoff levels of 400 and 600 nmol/L for the most preterm infants (as described in the “Methods” section), the overall positive predictive value was 3%. For the direct assay of 17-OHP, a cutoff level of 500 nmol/L would generate the same number of missed cases as the presently used cutoff level (200 nmol/L after extraction). The positive predictive value then would be 9.7%. With a cutoff at 450 or 400, the positive predictive value would be 6.7% or 4.5%, respectively.

Table 2 lists all infants in Sweden who had CAH and were born preterm since the start of the screening program in 1986. The prevalence of CAH among preterm infants was 1 in 8000, which was not significantly different from the prevalence among full-term infants (1/10 000). The mutational spectrum was not significantly different from that of full-term infants, although no infants with the mildest mutation (V281L) were detected. The CYP21 genotype was not available for 2 infants. One was a boy born in week 35. He showed clear signs of salt loss at 10 days of age with dehydration; serum sodium, 130 mmol/L; serum potassium, 8.9 mmol/L; and plasma renin, 150 ng/mL/h. The other infant was a girl who had severe virilization of the external genitalia and initially was assigned the wrong gender. Two of the infants who were born in week 33 were monozygotic twins (genotype I172N/del). They had very different 17-OHP levels in samples taken on day 7. The larger twin, with a birth weight of 2500 g, had 840 nmol/L plasma (790 nmol/L after extraction), whereas the smaller one, with a birth weight of 1450 g, had 250 nmol/L by direct assay (380 nmol/L when the sample was retested) and 90 nmol/L after extraction. They had been treated in utero with glucocorticoids during weeks 30 to 32. In a second sample taken at 10

Fig 1. Screening 17-OHP levels in 6200 preterm infants. The 17-OHP levels, by direct analysis, correlated with the gestational ages. The box plot shows the median values and the 10th, 25th, 75th, and 90th percentiles. The extreme values are denoted *, and the outliers are denoted O.
days of age, both twins had 17-OHP levels above 700 nmol/L. The smaller twin showed signs of salt loss, with a sodium concentration of 132 mmol/L on day 16 and elevated potassium on several occasions. Only 1 patient was born in gestational week 36 with a less severe form of CAH (genotype I172N/I2 splice, associated with the SV form of CAH). Her screening value was much lower than the cutoff level for infants who were born in week 36. She was detected because, at the first screening, the laboratory was informed that she had been born in week 37. Setting a cutoff level at 100 nmol/L for infants who were born during weeks 35 and 36 would pick up this patient. This cutoff would yield approximately 38 additional recalls per year (30 in gestational week 35 and 8 in week 36). A cutoff of 150 nmol/L would yield 6 or 7 more recalls per year (5 in week 35 and 1 or 2 in week 36). In the latter situation,
the patient with the I172N/I2 splice genotype would have been missed.

For 88 preterm infants who were born before week 33, information was available as to whether they had been treated prenatally with glucocorticoids. Prenatal treatment had been given in 60 cases, whereas 28 infants had not been treated. The screening 17-OHP levels in the 2 groups were not significantly different. The 17-OHP levels ranged between 15 and 270 nmol/L (median: 62 nmol/L, week 31) in the treated group and between 15 and 182 nmol/L (median: 50 nmol/L, week 31) in the untreated infants. Infants who were born in and later than week 30 had a median 17-OHP value that was lower in the prenatally treated group, but in infants who were born before week 30, the median 17-OHP screening value was higher in the treated group. There still was no difference between the groups when only infants who had received treatment within 3 days of the sample collection were included. Sixty-five of the infants were delivered by cesarean section, and 23 were delivered vaginally. As a group, the infants who were delivered by cesarean section had a slightly lower median screening value, but there was complete overlap between the groups. There was no systematic pattern for the screening value and a low Apgar score. In 3 infants, the sampling day had been later than day 8. It was day 13 with a 17-OHP level of 29 nmol/L, day 14 with a level of 59 nmol/L, and day 16 with a level of 41 nmol/L. Thus, we could not demonstrate any systematic influence of any of the studied interfering factors on the screening levels of 17-OHP.

**DISCUSSION**

It is widely known that it is difficult to interpret the result of a CAH screening test when the patient is born preterm. The spread of 17-OHP values among preterm infants also was very large, especially for infants born more prematurely. Even when gestational age–related cutoff levels were used, the false-positive rate was high and the predictive value of a positive test was as low as 3%. The balance between a high cutoff level, giving a higher specificity but a lower sensitivity, and lower cutoff levels, resulting in larger numbers of false-positive tests but fewer missed cases, is delicate. Both the adverse psychological effects on the families of a false-positive test result and the economic costs to the health care system have to be considered.32,33 Ether extraction has been used to increase the specificity of the screening procedure in preterm infants. It reduces the levels of interfering metabolites in the sample and thereby decreases the 17-OHP.
values. We found that the difference in 17-OHP levels with or without extraction was larger for infants who were not affected by CAH, making the difference between false- and true-positive values more distinct. However, a cutoff level of 400 or 500 nmol/L in direct analysis would give similar numbers of false-positive cases as the currently used recall levels. The same numbers of CAH patients would be detected. The advantage of the direct procedure obviously is that recall times can be shortened considerably, which is essential to avoid a salt crisis. Using our current procedure, the age at recall was 13 days (median) for the preterm infants, compared with 8 days for the full-term infants, which reflects the extra time that it takes to go through the extraction procedure. Omitting this procedure also would reduce the costs of screening considerably.

Infants who are treated prenatally with glucocorticoids to induce pulmonary maturation might show depressed 17-OHP levels during the first week of life.26,27 Consequently, there is a risk of false-negative as well as false-positive tests when screening preterm infants. In this study, we could not demonstrate any systematic influence of prenatal glucocorticoid treatment or perinatal stress factors on the screening levels of 17-OHP. This probably is because many different factors affect the 17-OHP screening values in preterm infants, eg, interfering metabolites, prenatal glucocorticoid treatment, stress, and the very unpredictable and individual response to stress caused by immaturity.28,29 The monozygotic twins with CAH, who had very different 17-OHP levels in the first screening test, clearly illustrate that the suppressive effect of prenatal glucocorticoid treatment on the pituitary varies in both extent and duration from individual to individual. Thus, it is impossible to construct recall levels that take all of these different factors into account.

The European Society for Paediatric Endocrinology group for neonatal screening has suggested that a second sample be taken for all preterm infants at 14 days of age to overcome the problem with false-negative results due to treatment with steroids.34 It is most likely, however, that new recall levels would have to be determined for these circumstances because those currently used have been developed for newborn infants at the age of 3 to 5 days. If one relies on a later second sample, then it is crucial that early signs of salt loss be recorded carefully. When using a second sample, it is possible that more children with milder forms of CAH would be diagnosed. In Texas, where a second screening sample is taken from all newborns at 2 weeks of age, it has been documented that a higher percentage of patients with milder forms of the disease are detected by this approach.24 The 17-OHP levels in untreated infants with CAH increase over time in the neonatal period, whereas they decrease in healthy infants.23,25 However, the most important aim of the screening program is to identify patients with the severe forms of CAH, to avoid a salt-losing adrenal crisis and to prevent early death, as well as to achieve earlier correct gender assignment in virilized girls. Patients with mild CAH certainly should be offered early treatment to normalize growth and pubertal development. However, it remains to be established that all patients with mild CAH would benefit from receiving a diagnosis and being treated neonatally, because the natural course of the disease is not well known in this group of patients. There might be risks associated with overtreatment of patients with the mildest forms of the disease, and we know little about any possible risks associated with suppressing the adrenals during critical periods in development. The number of patients with a late diagnosis is low in Sweden; thus, it is not likely that a large number of children with mild CAH are missed in screening. We also believe that our systems for follow-up, including well-infant clinics, are reasonably well suited for detecting early signs of androgen excess manifested in mildly affected patients.

Twelve children with CAH have been born preterm in Sweden since the initiation of the screening program in 1986 (Table 2). Eight of them had their CAH diagnosed in the screening procedure, whereas 4 were missed. Overall, the patients with the less severe forms of the disease (with genotypes including the I172N mutation) had lower 17-OHP values. The I172N mutation is associated with varying degrees of prenatal virilization, and approximately 10% of patients with this genotype develop SW symptoms.3 We found that the 17-OHP levels reflected the disease severity rather than the gestational age. This is in agreement with our previous findings in full-term infants.31 In the latter study, the 17-OHP levels reflected disease severity when the patients were grouped according to genotypes, although there was overlapping between the groups and an individual sample could not be used for prognostic purposes. No preterm patients with the V281L mutation, the most common cause of mild CAH, had their CAH diagnosed in the screening program. In our experience, children with genotypes including this mutation are not at risk of developing SW symptoms, do not present with prenatal virilization, and therefore are not primary targets for the screening.

One way of improving the screening procedure is to include CYP21 mutation analysis directly from the dried filter-paper blood spots in all cases with elevated 17-OHP levels.36 The specificity but not the sensitivity of the procedure would be improved in this way. Thus, an analysis of the 9 most common mutations would confirm the diagnosis in the vast majority of the infants who had CAH and an elevated 17-OHP level in the first screening sample. This procedure also would obviate the need for a second blood sample, which would eliminate many of the psychological problems and the costs involved. Obviously, the problem with the false-negative screening tests would remain, unless genetic screening were included in the screening of all preterm infants.

On the basis of the results of this study, we have decided to change our routines for the neonatal screening of CAH in preterm infants. From having used a recall level of 200 nmol/L plasma after extraction, we have chosen to use a cutoff level of 400 nmol/L in direct analysis for infants who are born
before week 35. To detect more patients, the cutoff level would have to be very much lower, which would result in a number of recalls that we would consider to be unacceptably high. In our study population, no infants with CAH were born before week 32. We assume that the same cutoff level could be used for these infants. For infants who are born in weeks 35 and 36, a cutoff level of 400 nmol/L would detect the same number of patients as the one we have used so far. However, the presently used protocol missed a patient who had less severe CAH and was born in week 36. Therefore, we have chosen to use 150 nmol/L as the cutoff for infants who are born in weeks 35 and 36, a procedure estimated to increase the number of recalls by 6 or 7 per year (<10/100,000 newborns). With this novel algorithm, we will have approximately the same number of false-positive tests as we do with the present procedure, but we will gain considerably in time and cost by omitting ether extraction. This will be of benefit to the patients and their families. We will detect patients with the most severe forms of CAH, null and I2 splice genotypes (SW). However, the risk of missing some patients with the SV form and a large portion of the patients with the nonclassic form of the disease in the screening for preterm infants persists. The results of these new algorithms will be evaluated continuously.

Screening for CAH has clear benefits for full-term infants.16,24,37 The situation of preterm infants is considerably more complicated, with an increased risk of false-positive as well as false-negative screening results. The screening protocol of choice for preterm infants is dependent primarily on local factors, such as the possibility of later follow-ups. Under all circumstances, it is important to emphasize that not all patients with CAH, regardless of whether they were born preterm or full term, can be identified through screening. A number of the patients with milder forms of the disease will still have to be diagnosed on the basis of clinical signs and symptoms.

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