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The First-Year Outcomes of the Nationwide Neonatal CAH Screening in Türkiye: High Rate of False Positives for 21-Hydroxylase Deficiency and a Higher Detection Rate of Non-Classical Cases

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What is already known on this topic?

Salt-wasting 21-hydroxylase deficiency congenital adrenal hyperplasia (21-OHD CAH) is a recessive disorder that can lead to high mortality if treatment is not initiated early. Neonatal screening, particularly in males and in groups with limited access to healthcare, reduces mortality and morbidity associated with 21-OHD CAH. In Türkiye, neonatal CAH screening began with pilot studies in 2017 and gradually expanded to become nationwide in 2022.

What this study adds?

The prevalence of classical 21-OHD CAH in the nationwide CAH screening in Türkiye is 1:12,044. Implementing updated cutoffs will help reduce false positives, lower neonatal screening costs, and prevent the detection of non-classical CAH cases.

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Abstract

Objective: Neonatal screening for congenital adrenal hyperplasia (CAH) was implemented nationwide in Türkiye in 2022. The performance of this screening program in its first year was assessed.

Methods: This retrospective, descriptive study included neonates born in Türkiye between January 1 and December 31, 2022, with gestational age ≥32 weeks and birth weight ≥1500 grams. The screening protocol used a two-tier approach. In the first step, 17α-hydroxyprogesterone (17-OHP) levels were measured using fluoroimmunoassay (FIA) in dried blood spots (DBS) collected at 3-5 days of life. Infants with positive results underwent second-tier testing using liquid chromatography-tandem mass spectrometry to measure 17-OHP, 21-deoxycortisol (21-DF), cortisol (F), and 11-deoxycortisol (S) in DBS. Those with a steroid ratio (21-DF + 17-OHP)/F ≥1 were referred to pediatric endocrinology clinics for diagnostic evaluation.

Results: Of 1,096,069 neonates screened (including 149,652 refugees), second-tier tests were performed on 70,455 (6.88%) infants, and 3,429 (0.27%) were referred to clinics, resulting in 91 confirmed cases of classical 21-hydroxylase deficiency (21-OHD) CAH (77; salt-wasting, 14; simple virilizing). Twenty-two patients were diagnosed with non-classical 21-OHD CAH. The frequency of classical 21-OHD was 1 in 12,044. The first-tier FIA-17-OHP values were below 17.5 ng/mL in 99.8% of healthy neonates with ≥36 weeks gestation or ≥2500 grams and below 50 ng/mL in those with 32-36 weeks or 1500-2500 grams.

Conclusion: Neonatal CAH screening facilitates early diagnosis of 21-OHD and improved patient care. Using refined cut-offs may reduce referrals six-fold and eliminate second-tier testing for 95% of infants. Ongoing evaluation can enhance the efficiency and cost-effectiveness of the screening protocol.

Keywords: Neonatal screening, congenital adrenal hyperplasia, second-tier, steroid profiling, LC-MS/MS

Introduction

Neonatal screening (NS) for congenital adrenal hyperplasia (CAH) reduces mortality and morbidity associated with classical 21-hydroxylase deficiency (21-OHD). Therefore, it is included in the NS programs of many developed countries and is recommended by international guidelines (1).

Although novel, molecular-based CAH screening methods, such as long-read sequencing, show promise, hormone measurement-based screening methodologies, particularly those utilizing mass spectrometric steroid profiling, remain highly sensitive in the early diagnosis of the condition (2,3). Consequently, current practices favor two-tiered screening programs, with the second-tier employing liquid chromatography-tandem mass spectrometry (LC-MS/MS) (1).

In Türkiye, CAH has been included in the NS program since 2017. The second-tier of the program involves measuring 17α-hydroxyprogesterone (17-OHP), 21-deoxycortisol (21-DF), cortisol (F), and 11-deoxycortisol (S) in dried blood spots (DBS) using LC-MS/MS and Türkiye is one of the first countries in the world to adopt this approach. Of note, the inclusion of 21-DF and S in the second-tier testing not only reduces the false positivity of the screening but also facilitates the differentiation of rare CAH forms that may present with elevated 17-OHP levels (4). This feature is particularly important in countries like Türkiye, where consanguineous marriages are common, to effectively identify the targetted patient for screening. However, in contrast to many other countries that use the dissociation-enhanced lanthanide fluoroimmunoassay method to measure 17-OHP in the first step of screening, the fluoroimmunoassay (FIA) method was employed for economic reasons. FIA-17-OHP cut-off values of 10 ng/mL and 15 ng/mL were used in the first step of screening for newborns ≥36 weeks and/or ≥2500 g, and for those 32-36 weeks and/or 1500-2500 g, respectively. The cut-off values used in the screening were determined based on examples from previous screening programs (3,5). Audits of the pilot NS for CAH conducted in Türkiye between 2017 and 2022 were used to analyze false-positive (FP) rates and overall effectiveness (6,7). The aim of this study was to evaluate the outcomes of the first year of the nationwide neonatal CAH screening program, which was expanded to cover the whole country in 2022, and to develop strategies for improvement based on the identified pitfalls.

Methods

A retrospective, cross-sectional study was conducted based on reports generated from the screening program database, including all newborns screened under the authority of Turkish Directorate of Public Health (TDPH) from 1 January to December 31, 2022.

DBS samples were collected on filter paper ("Guthrie" cards) between the third and fifth days of life by heel prick, at public health units, general hospitals, and maternity hospitals. The CAH screening algorithm is presented in Figure 1.

Initial CAH screening was based on the measurement of 17-OHP in DBS on filter paper by FIA (Labsystems Diagnostics, Finland). If the 17-OHP level exceeded the cut-off in the first-tier immunoassay, the filter paper was analyzed using LC-MS/MS for a steroid profile of 17-OHP, 21-DF, F, and S (6,7). Normal values were: for neonates 32-36 weeks and/or 1500-2500 g, 17-OHP < 8 ng/mL, 21-DF < 1.5 ng/mL, F > 50 ng/mL, S < 1.8 ng/mL; for neonates ≥36 weeks

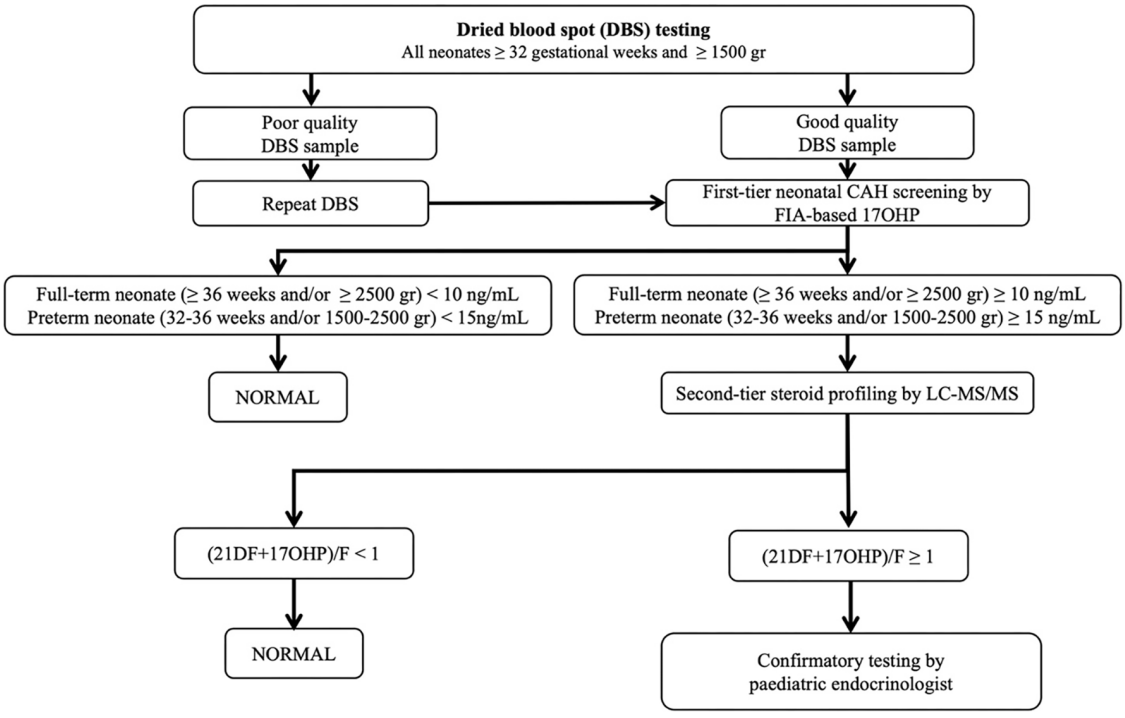

Figure 1. The flowchart of neonatal CAH screening, which became nationwide in Türkiye in 2022. Screening is carried out in Türkiye in all newborns above 32 weeks of gestation and 1500 g birth weight with a single sample two-tier testing strategy

CAH: congenital adrenal hyperplasia, FIA: fluoroimmunoassay, 17OHP: 17α-hydroxyprogesterone, LC-MS/MS: liquid chromatography-tandem mass spectrometry, 21DF: 21-deoxycortisol

and/or ≥2500 g, 17-OHP < 1.5 ng/mL, 21-DF < 1.5 ng/mL, F > 50 ng/mL, S < 1.8 ng/mL. A (21-DF + 17-OHP)/F ratio ≥1 and/or S > 10 ng/mL were the main criteria for referral for further clinical evaluation for 21-OHD and 11β-hydroxylase deficiency (11β-OHD) CAH, respectively.

Classical CAH was defined as an elevated 17-OHP level confirmed by retest and/or clinical evaluation, followed by genotyping. False positives were characterized by the absence of genital abnormalities and/or salt-wasting (SW), with normal 17-OHP levels on retest. The clinical, laboratory, and genetic investigation results of infants diagnosed with CAH were collected from the centers where they were followed after referral to clinics. We also collected information from the centers on which type of 21-OHD, SW, simple virilizing (SV) or non-classical (NC) the patients diagnosed with CAH had. SW CAH is the most severe form, caused by complete enzyme deficiency, leading to low cortisol and aldosterone, and high androgen levels, resulting in prenatal virilization of females. Without treatment, infants may die within weeks due to SW crisis. SV CAH, with mild residual 21-OH activity (1-5%), has sufficient aldosterone to prevent salt loss but still requires glucocorticoid treatment for cortisol deficiency and androgen excess. NC CAH, with 30–50% enzyme activity, maintains normal cortisol and aldosterone but has elevated androgens, typically diagnosed in childhood or young adulthood due to symptoms of androgen excess (8).

Final calculations of true-positive (TP), FP, true-negative (TN) and false-negative (FN) screening results were recorded. Efficiency of screening protocol was assessed with positive predictive value (PPV), sensitivity and specificity, calculated using the following formulae: PPV = TP/(TP + FP), sensitivity = TP/(TP + FN), specificity = TN/(TN + FP). Although it is not always possible to reach babies born in the country, especially refugee babies, data from the TDPH were compared with data from pediatric endocrine centers, and data from the TDPH were reviewed by a member of a NS scientific advisory committee (TG) to reduce FN and TN rate.

Ethics

The parents were informed about Turkish newborn screening. Heel-prick blood samples were collected from live-born babies after written consent from the parents was obtained. The study was carried out with the written permission of the Scientific Committee of the TDPH.

Statistical Analysis

Statistical evaluation was performed using GraphPad Prism® V9.0 software (GraphPad Software Inc., San Diego, California, USA). The results for each steroid are reported as mean, standard deviation or as median (interquartile range) in the text. We performed a t-test for the comparison of the means of two independent samples. Values were considered statistically significant when the p value was less than 0.05.

Results

The total number of newborns who underwent CAH screening was 1,096,069 (including 149,652 refugees). Of these babies, 1,015,200 (92.6%) were ≥36 gestational weeks and/or ≥2500 g birth weight. Of these infants, 70,455 (6.9%) underwent second-tier testing because their FIA-17-OHP levels were above the first-tier cut-off values.

For healthy infants without a final diagnosis of CAH, the 99.8th percentile values for first-tier FIA-17-OHP measurements were found to be below 50 ng/mL for those with a gestational age of 32-36 weeks and/or a birth weight of 1500-2500 g, and below 17.5 ng/mL for those with a gestational age of ≥36 weeks and/or a birth weight of ≥2500 g.

Neonates, who failed to pass second-tier testing (3,429 of 70,455; 4.8%); were referred to pediatric endocrinology clinics for further evaluation, which corresponds to an overall recall rate of 0.31%. The average number of days for referral of neonates to the clinic was 11.75 ± 6.05 days. Consequently, 113 neonates were diagnosed with CAH (55 females, 58 males). Seventy-seven were diagnosed as classical SW 21-OHD CAH, while 14 were SV and 22 were NC 21-OHD CAH. Second-tier testing results of SW, SV and NC-21-OHD CAH patients diagnosed by NS are presented in Supplementary Table 1a, b and c, respectively.

The distribution of 21-OHD CAH forms by sex is shown in Table 1, and no differences in prevalence of forms were observed between the sexes. The incidence of classical 21-OHD in the screened population was 1:12,044. None of these babies was premature nor had low birth weight. Out of the 91 neonates diagnosed with classical CAH through screening, 17 (15%) were refugees, and all of these cases were of the classical SW type.

Table 1. The distribution of 21-OHD CAH forms by sex

	Female	Male	Total
Salt-wasting	38 (69%)	39 (67%)	**77**
Simple virilizing	5 (9%)	9 (16%)	**14**
Non-classical	12 (22%)	10 (17%)	**22**
Total	**55**	**58**	**113**

21-OHD CAH: 21-hydroxylase deficiency congenital adrenal hyperplasia

In all infants diagnosed with classic 21-OHD, the (21-DF + 17-OHP)/F ratio was above 2. Overall, the PPV, sensitivity and specificity of the current screening protocol for classical 21-OHD CAH was calculated as 2.5, 100 and 99.6%, respectively. There was no FN case.

Out of 113 patients diagnosed with CAH, a molecular diagnosis was achieved in 64 patients. Forty-five (70%) patients were homozygous, 14 (22%) were compound heterozygous carriers of *CYP21A2* pathogenic variants, and 5 (8%) patients had a single pathogenic allele identified. The distribution of a total of 149 detected alleles, according to their frequency and severity, is shown in Figures 2A and 2B.

We were unable collect the number of patients with biochemically/genetically confirmed 11β-OHD from the centers.

Discussion

This audit presents the first evaluation of the nationwide neonatal CAH screening programme in Türkiye. The most significant finding of the analysis, as we previously recommended in our pilot studies, is the need to increase the cut-off values for FIA-17-OHP used in the first-tier screening. This approach will reduce the number of FP cases referred to the clinic in particular and thus decrease the number of cases subjected to second-tier testing, thereby lowering the screening costs.

In line with our previous findings (6,7), if the cut-off values of 50 ng/mL for neonates with a gestational age of 32-36 weeks and/or a birth weight of 1500-2500 g, and 17.5 ng/mL for those with a gestational age of ≥36 weeks and/or a birth weight of ≥2500 g, had been used for first-tier FIA-17-OHP measurements, the number of infants subjected to second-tier screening would have been 3,596 instead of 70,455. Even with this proposed approach, 95.1% of the samples subjected to second-tier screening would not have needed this step. This will result in significant savings in both workload and costs.

Currently, in the second-tier of the screening programme, neonates with an LC/MS-MS-based (21-DF + 17-OHP)/F≥1 are referred to clinics for assessment for classical CAH. This cut-off value was determined based on the results of a previous study that retrospectively examined DBS samples (9). However, both in this current nationwide screening analysis and in previous pilot CAH screening trials in Türkiye, all patients diagnosed with classical CAH had a second-tier (21-DF + 17-OHP)/F ratio greater than 2 (6,7). If a (21-DF + 17-OHP)/F ratio of ≥2 had been used instead of ≥1

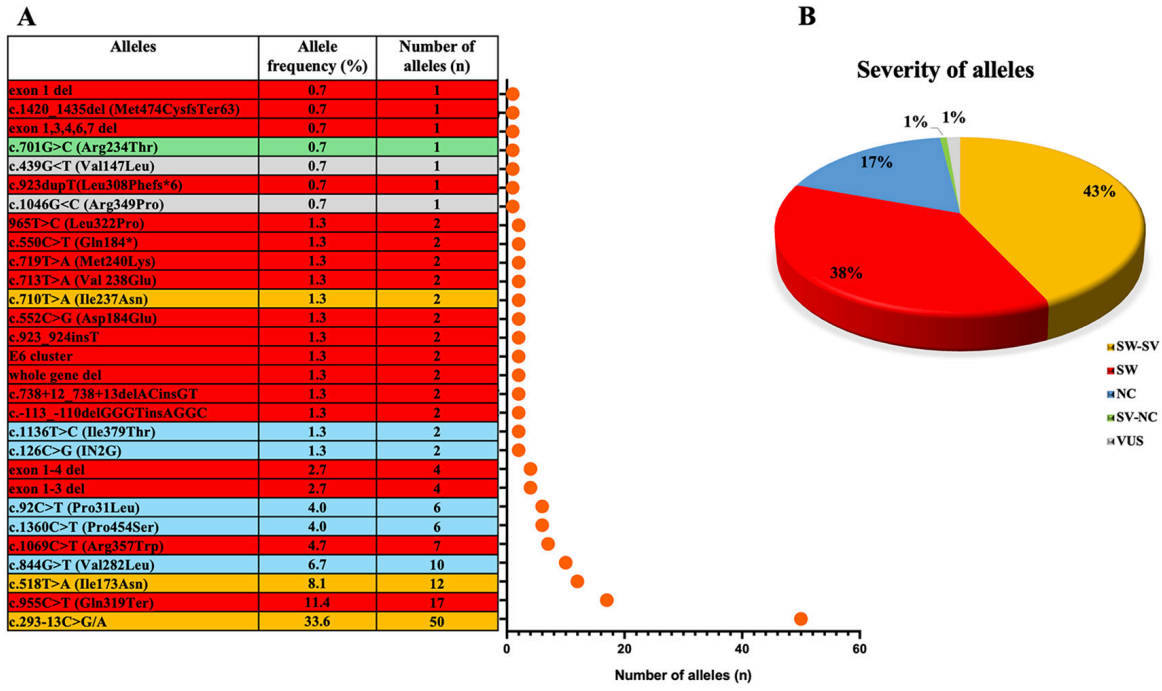

Figure 2. Distribution of the severity and frequency of *CYP21A2* variants detected in patients diagnosed in the first year of the nationwide neonatal CAH screening in Türkiye. **A)** Specific *CYP21A2* variants are indicated by allele frequency and allele numbers and highlighted in red, orange, blue, yellow and grey according to clinical severity representing salt-wasting, salt-wasting-simple virilising, non-classical, simple virilising-non-classical and variant of unknown significance, respectively. Prevalence of the variants are shown in the frequency dot plot graph on the right. **B)** A pie chart shows the frequency of all alleles detected in diagnosed CAH patients according to their clinical effects

SW: salt-wasting, SV: simple virilising, NC: non-classical, VUS: variant of unknown significance, CAH: congenital adrenal hyperplasia

as the referral criterion in the current screening, there would have been 563 referrals (about 1/6 of all referrals) instead of 3,429. This means that the recall rate in the screening would have been 0.051 % instead of 0.31 %. Therefore, the PPV would have increased by up to 16 %.

An additional concern is the detection of NC CAH cases through NS. The detection of some NC CAH cases can be explained by the low cut-off values used in first-tier 17-OHP measurements. NC CAH cases identified through screening do not reflect the true prevalence of NC-CAH and these neonates should be monitored without treatment unless a clear indication for treatment arises.

One area that requires improvement is the recall time. The success of screening depends on detecting the patient before symptoms develop. In SW CAH, symptoms are expected to begin after the first week of life. DBS samples in the current screening are collected after 72 hours postnatally. If the neonate is discharged before 72 hours, a heel-prick blood sample is taken by contacting the family through their affiliated primary healthcare provider. Delays in processes, such as reaching the family or the family's attendance at the healthcare facility, can prolong the recall time in some cases. This particularly creates challenges in reaching the babies of migrant families living in Türkiye, who constitute approximately 1/7 of all screened neonates. Since the second-tier screening uses LC-MS/MS with very low hormone interference, we recommend a pilot study to analyse false positives and false negatives in DBS samples collected before discharge. If there is no negative impact on screening results, moving the DBS collection to before discharge may shorten the recall time. As we suggested in previous pilot studies, referring neonates with very high first-tier test results (i.e., FIA-17-OHP > 90 ng/mL) to clinical evaluation without undergoing second-tier testing would also shorten the time to diagnosis, especially in SW cases.

Patients were diagnosed with classic CAH based on clinical findings (ambiguous genitalia and/or salt loss) in addition to a positive screening test, and the diagnosis was confirmed by biochemistry and further hormone testing. Inadequacies in accessible genetic testing, such as the inability to perform multiplex ligation-dependent probe amplification testing in all patients as molecular evidence, or that only the 10 most common mutations leading to 21-OHD were examined,

may have led to the failure to find the pathogenic second *CYP21A2* allele in some patients.

Study Limitations

One limitation of this audit is the inability to reliably determine steroid hormone cut-off levels that define subgroups of 21-OHD in diagnosed patients. This is due to the differences in the variants carried by the patients and the relatively small number of diagnosed cases. Furthermore, although second-tier CAH screening strategy would facilitate identification of cases with 11β-OHD, we were unable collect the number of patients with biochemically/genetically confirmed 11β-OHD from the centers. Therefore, we could not include data on the prevalence of 11β-OHD in this study.

Conclusion

As the Neonatal CAH Screening Scientific Committee, we believe that implementing the aforementioned changes during the early phase of the nationwide expansion of screening will enhance its long-term effectiveness and cost-efficiency, while also reducing laboratory and clinical workload. Furthermore, we consider that such audits in newborn screening programmes are crucial for improving preventive healthcare services.

Ethics

Ethics Committee Approval: The study was carried out with the written permission of the Scientific Committee of the TDPH.

Informed Consent: Heel-prick blood samples were collected from live-born babies after written consent from the parents was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Tülay Güran, Concept: Tülay Güran, Elif Yürüker, Ahmet Anık, Müge Atar, Emine Çamtosun, Elif Eviz, Mehmet İsakoca, Eda Mengen, Büşra Gürpınar Tosun, İhsan Turan, Aylin Kılınç Uğurlu, Edip Ünal, Doğuş Vurallı, Gülay Can Yılmaz, Yüksel Hakan Aydoğmuş, Şükran Darcan, Design: Tülay Güran, Şükran Darcan, Data Collection or Processing: Tülay Güran, Elif Yürüker, Ahmet Anık, Müge Atar, Emine Çamtosun, Elif Eviz, Mehmet İsakoca, Eda Mengen, Büşra Gürpınar Tosun, İhsan Turan, Aylin Kılınç Uğurlu, Edip Ünal, Doğuş Vurallı, Gülay Can Yılmaz, Yüksel Hakan Aydoğmuş, Şükran Darcan, Analysis or Interpretation: Tülay Güran, Literature Search: Tülay Güran, Writing: Tülay Güran.

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