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Incidence analysis of six diseases in the national newborn screening program: a retrospective study from Adıyaman, Turkiye (2019-2023)

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ABSTRACT

Aims: This study aimed to determine the incidence of diseases included in the national newborn screening program in Adıyaman, Turkey, over the past five years and to evaluate the relative status of Adıyaman compared to national and global data. The study also sought to identify potential risk factors based on demographic variables.

Methods: A retrospective, descriptive study was conducted in Adıyaman, Southeastern Turkey, analyzing heel blood sample data from 52,964 newborns between 2019 and 2023. The study excluded cases with unsuitable or retaken heel blood samples, partial biotinidase deficiency, and partial phenylalaninemia. Annual incidence rates were calculated based on confirmed diagnoses from relevant clinics.

Results: The five-year incidence rates in Adıyaman were found to be higher than the national averages for phenylketonuria (1:2407), congenital hypothyroidism (1:582), biotinidase deficiency (1:481), cystic fibrosis (1:10593), congenital adrenal hyperplasia (1:5864), and spinal muscular atrophy (1:9489). No statistically significant differences were identified based on gender, birth weight, birth week, or maternal nationality, except for biotinidase deficiency, which was significantly higher in infants of Turkish mothers.

Conclusion: The study highlights a higher incidence of screened diseases in Adıyaman than national averages, particularly biotinidase deficiency. Further research is recommended to investigate these findings and to address potential causes, such as consanguineous marriages.

Keywords: Newborn screening, phenylketonuria, biotinidase deficiency, congenital hypothyroidism, incidence

INTRODUCTION

Newborn screening programs are globally implemented for various diseases. Examples of these diseases include hearing impairment, developmental hip dysplasia, endocrine and metabolic disorders, and genetically inherited diseases such as spinal muscular atrophy.[1-3] The criteria for screening a disease were defined by Wilson and Jungler in 1968, and many of these are still in use today. These criteria include the disease being a significant public health issue, having effective treatment available, the screening test being feasible to apply, and being acceptable to society.[4] From a public health perspective, newborn screening programs constitute a critical group within secondary prevention programs. When diagnosed early, the diseases screened in this group generally progress with minimal impact on the individual and society through low-cost treatments and precautions. Individuals who are not diagnosed early may become entirely dependent.[5] This program, which enhances the quality of life for society and individuals, was first implemented in Turkiye for phenylketonuria in 1987 and was nationally expanded in 1993. Later, in 2016, with the addition of hypothyroidism to the screening program, it was named the national newborn screening program. The program was expanded to include six diseases with the addition of biotinidase deficiency in 2008, cystic fibrosis in 2015, and congenital adrenal hyperplasia and spinal muscular atrophy in 2022.[6]

The history of neonatal screening programs is not very old. The first implementation of screening programs can be traced back to 1957 when phenylpyruvic acid was tested in urine. Later, in 1959, phenylalanine levels in the blood were measured, but the test became widely applicable in 1961 when Dr. Guthrie developed the method using a few

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drops of blood from a newborn's heel. Four years later, all newborns in New York State, USA, began to be screened for phenylketonuria.[7] While many countries implement newborn screening programs, approaches to screening programs and the diseases screened can vary. Countries such as Saudi Arabia, the Netherlands, New Zealand, and the UK run national programs, while Australia, Canada, and Sweden implement them at a regional level. Many countries continue the implementation, but the mentioned countries grant regional discretion in their application methods. The content of screening programs also varies globally. Six diseases are currently screened in Turkey, 13 in the UK, 20 in Singapore, 21 in Japan, 24 in Saudi Arabia, 27 in Australia, 30 in Canada, and 36 diseases are screened in the USA.[1,8] The number of diseases screened in developed countries is significantly broader than in our country.

In countries like Turkiye, where consanguineous marriages are common, the need for neonatal screening programs is better understood, considering that genetic, metabolic, and endocrine disorders are more likely to develop. Like other countries with similar marriage traditions, Turkiye continues its efforts to include other diseases in the screening programs.[3,6] To understand the significance of consanguineous marriages, it is worth noting a 2022 study that examined infant mortality in Adıyaman, where 26% of infant deaths were found to be associated with parental consanguinity.[9] The percentage of newborns screened in Turkiye increased from 53% in 1998 to 88% in 2008, and according to the latest data from the Ministry of Health, currently, 97% of newborns in the country are screened for six diseases.[10] Among the diseases screened in Turkiye, congenital hypothyroidism is the most common worldwide, with an incidence of 1:3500-4000 globally, while in Turkey, it is found to be 1:3344. In Turkiye, phenylketonuria is most frequently observed, with an incidence of 1:4500.[3]

This study aims to determine the incidence of diseases included in the neonatal screening program over the past five years, to assess the relative status of Adıyaman compared to Turkiye and world data, and to evaluate any risk factors for the screened diseases according to demographic data. A literature review reveals that incidence studies have been conducted in several provinces in Turkey. However, no study has examined all six diseases in the more traditional culture of the Southeastern Anatolia Region. We believe this study will fill a gap in the literature.

METHODS

This retrospective-descriptive study was planned in Adıyaman province, located in the Southeastern Anatolia Region of Turkey.

Ethical approval for the study was obtained from the Non-interventional Researches Ethics Committee of Fırat University (Date: 14.12.2023, Decision No: 2023-14/32). Due to the study's retrospective nature, patient consent was not obtained, but institutional permission to use the data was obtained from the Adıyaman Provincial Health Directorate. The study adhered to the principles of the Helsinki Declaration.

Heel blood samples from newborns born in hospitals are taken within the first 48 hours in the hospital where the birth occurs before the patient is discharged. The second heel blood sample is taken at Family Health Centers 48-72 hours after the newborn starts oral feeding. Newborns with values above the upper limit in the heel blood results are referred to the relevant clinic by family physicians for diagnosis and treatment. This process is usually completed within approximately 15 days. For newborns with borderline values, heel blood is taken again, and the process continues. Diagnostic values are specified in **Table 1**.

Table 1. Reference values used in evaluating the results of diseases screened under the national newborn screening program

	Normal		Repeat heel blood[a]/Advanced analysis from the same sample[b]/ Venous blood sample[c]	Referral
PKU - Phenylalanine level	≤2 mg/dl		2,1-3,9 mg/dl[a]	≥4 mg/dl or ≥21 mg/dl after repeat blood sample
CH-TSH value	<5,5 mlU/L		5,5-20 mlU/L[a]	>20 mlU/L or ≥55 mlU/L after repeat blood sample; refer to appropriate lab for serum T4, TSH test, depending on the physician's opinion
BD – Biotinidase enzyme activity	>65 U		≤65 U[a]	≤65 U after repeat blood sample
CF-Blood immunoreactive trypsinogen (IRT) value	<90 µg/L		≥90 µg/l[a]	≥70 µg/L after repeat blood sample
CAH-17-hydroxyprogesterone first-step analysis	For babies ≥36 weeks and ≥2500 g	<10 ng/ml	≥10 ng/ml[b]	≥10 ng/ml; in the second-step analysis from the same sample, 21-deoxycortisol + 17-hydroxyprogesterone/cortisol ≥ 1 and/ or 11-deoxycortisol ≥ 10 ng/mL
	For preterm babies 32-35 weeks and 1500-2499 g	<15 ng/ml	≥15 ng/ml[b]	
SMA-SMN1 gene molecular analysis	No mutation		Suspicious[c]	Homozygous mutation; or refer to neurology if a homozygous mutation is confirmed by dry blood spot analysis

PKU: Phenylketonuria, CH-TSH: Congenital hypothyroidism-thyroid stimulating hormone, BD: Biotinidase deficiency, CF: Cystic fibrosis, CAH: Congenital adrenal hyperplasia, SMA: Spinal muscular atrophy, SMN1: Survival motor neuron 1

Table 2. Number of births, diagnosed cases from screened diseases, and incidences of screened diseases by year

	Births	PKU		CH		BD		CF		CAH		SMA	
	n	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence	n	Incidence
2019	11 915	6	1:1986	28	1:426	30	1:397	-	-	-	-	-	-
2020	11 056	3	1:3685	18	1:614	34	1:325	1	1:11056	2	1:5528	-	-
2021	11 015	7	1:1574	14	1:787	16	1:688	1	1:11015	-	-	-	-
2022	10 386	3	1:3462	27	1:385	14	1:742	3	1:3462	4	1:2597	1	1:10386
2023	8 592	3	1:2864	4	1:2148	16	1:537	-	-	1	1:8592	1	1:8592
Total	52 964	22	1:2407	91	1:582	110	1:481	5	1:10593	7	1:5864	2	1:9489

PKU: Phenylketonuria, CH: Congenital hypothyroidism, BD: Biotinidase deficiency, CF: Cystic fibrosis, CAH: Congenital adrenal hyperplasia, SMA: Spinal muscular atrophy

All newborns who had heel blood taken in Adıyaman between 2019 and 2023 were included in the study. Thus, the sample size represents the entire population. During data analysis, heel blood samples that were improper and had to be retaken were excluded. Newborns with partial biotinidase deficiency and partial phenylalaninemia were also excluded. The annual and five-year incidences of the diseases were calculated by dividing the number of diagnosed individuals by the number of individuals at risk (number of births) within the specified time period. Birth numbers were obtained from the Turkish Statistical Institute (TÜİK) data. The treatment status of the babies was not questioned, and the annual incidence was calculated based on the babies diagnosed by the relevant clinics. The researchers identified babies diagnosed through the Public Health Management System, and their diagnoses were confirmed through hospital records.

Statistical Analysis

The analyses were conducted using the SPSS (Statistical Package for Social Sciences; SPSS Inc., Chicago, IL) version 25 software package. Categorical data were presented as n (%), and numerical data were presented as median (min-max) values. The Pearson Chi-square test and Fisher Exact test were used for the comparison of categorical variables between groups. The normality of the distribution of numerical variables was assessed using the Kolmogorov-Smirnov test and visual methods (histogram and probability plots). For numerical data that did not follow a normal distribution, the Mann-Whitney U test was used for comparison between two independent groups. A p-value of less than 0.05 was considered statistically significant in all analyses.

RESULTS

The screening and referral results for six diseases conducted between 2019 and 2023 for newborns residing in Adıyaman province under the NCP were evaluated. As a result of the screenings conducted over these 5 years, 109 (0.2%) of the screened babies were referred for further investigation with suspicion of phenylketonuria, 551 (1.1%) for congenital hypothyroidism, 260 (0.5%) for biotinidase deficiency, 113 (0.2%) for cystic fibrosis, 80 (0.2%) for congenital adrenal hyperplasia, and 5 (0.03%) for spinal muscular atrophy. After referral, 22 babies were diagnosed with phenylketonuria (incidence: 1:2407), 91 with congenital hypothyroidism (incidence: 1:582), 110 with biotinidase deficiency (incidence: 1:481), 5 with cystic fibrosis (incidence: 1:10593), 7 with congenital adrenal hyperplasia (incidence: 1:5864), and 2 with type 1 spinal muscular atrophy (incidence: 1:9489). Among the diseases screened, biotinidase deficiency had the highest five-year incidence in Adıyaman province, while cystic fibrosis had the lowest (**Table 2**).

Table 3. Disease status of newborns screened between 2019-2023 by gender

		Gender (n=53 252)		
		Male, n (%)	Female, n (%)	p
PKU	Normal	27 047 (99.97)	26 147 (99.95)	0.472*
	Diagnosed	9 (0.03)	13 (0.05)	
CH	Normal	25 952 (99.85)	25075 (99.79)	0.083*
	Diagnosed	38 (0.15)	53 (0.21)	
BD	Normal	27 014 (99.8)	26 128 (99.8)	0.987*
	Diagnosed	56 (0.2)	54 (0.2)	
CF	Normal	26 822 (99.99)	58 (99.99)	0.682**
	Diagnosed	2 (0.01)	3 (0.01)	
CAH	Normal	18 904 (99.98)	18 245 (99.98)	1.000**
	Diagnosed	4 (0.02)	3 (0.02)	
SMA	Normal	8 000 (99.98)	7 991 (100.0)	0.500**
	Diagnosed	2 (0.02)	0 (0.0)	

* Chi-square test ** Fisher's exact test applied. PKU: Phenylketonuria, CH: Congenital hypothyroidism, BD: Biotinidase deficiency, CF: Cystic fibrosis, CAH: Congenital adrenal hyperplasia, SMA: Spinal muscular atrophy

The frequency of disease occurrence by gender was evaluated for newborns screened for six diseases between 2019 and 2023. No statistically significant difference was found in the diagnosis rates by gender for all screened diseases (p>0.05 for each comparison) (**Table 3**).

No significant difference was found when comparing the birth weeks and birth weights of those diagnosed and not diagnosed with the six diseases (p>0.05 for each comparison). Although the birth weights were not statistically significant, the birth weights

Table 4. Birth weights of newborns screened between 2019-2023 based on disease status

	Birth week					Birth weight				
	Normal		Case		p*	Normal		Case		p*
	n	median (min-max)	n	median (min-max)		n	median (min-max)	n	median (min-max)	
PKU	53 190	39.0 (23.0-43.0)	22	38.5 (36.0-40.0)	0.824	52 956	3200.0 (500.0-6000.0)	22	3070.0 (2700.0-3600.0)	0.361
CH	51 016	39.0 (32.0-41.0)	90	39.0 (23.0-43.0)	0.869	50 794	3200.0 (560-6000)	90	3145.0 (1310.0-4350.0)	0.193
BD	53 132	39.0 (23.0-43.0)	109	38.0 (32.0-42.0)	0.469	52 899	3200.0 (500.0-6000.0)	108	3155.0 (1084.0-4200.0)	0.179
CF	52 745	38.0 (36.0-40.0)	5	39.0 (23.0-43.0)	0.195	52 514	3200.0 (545.0-6000.0)	5	2930.0 (2360.0-3700.0)	0.474
CAH	37 181	39.0 (35.0-40.0)	7	38.0 (28.0-43.0)	0.639	37 181	3200.0 (1175.0-6000.0)	7	3000.0 (2100.0-3600.0)	0.279
SMA	15 991	38.5 (38.0-39.0)	2	38.0 (23.0-43.0)	0.901	15 991	3365.0 (2900.0-3830.0)	2	3195.0 (570.0-5750.0)	0.649

*Mann-Whitney U test was applied, min: Minimum, max: Maximum, PKU: Phenylketonuria, CH: Congenital hypothyroidism, BD: Biotinidase deficiency, CF: Cystic fibrosis, CAH: Congenital adrenal hyperplasia, SMA: Spinal muscular atrophy

of those diagnosed were lower than those not for all screened diseases (Table 4).

The frequency of disease occurrence among newborns was evaluated according to the district of residence of their mothers. No statistically significant difference was found for the six diseases screened by district of residence, and the frequency of disease occurrence was similar for those residing in the central district and other non-central districts (p>0.05 for each comparison).

The frequency of disease occurrence among newborns was examined according to the nationality of their mothers. No significant difference was found in the frequency of disease occurrence according to maternal nationality for five of the six diseases. However, a significant difference was found in biotinidase deficiency, where the frequency of disease occurrence was significantly higher in babies whose mothers were Turkish citizens (0.22%) compared to those whose mothers were non-Turkish citizens (0.02%) (p=0.009) (Table 5).

Table 5. Disease status of newborns screened between 2019-2023 by mother's nationality

		Nationality		
		Turkish, n (%)	Others, n (%)	p*
PKU	Normal	48925 (99.96)	4316 (99.95)	0.698**
	Diagnosed	20 (0.04)	2 (0.05)	
CH	Normal	47307 (99.81)	3759 (99.92)	0.199
	Diagnosed	88 (0.19)	3 (0.08)	
BD	Normal	48852 (99.78)	4337 (99.98)	0.009
	Diagnosed	109 (0.22)	1 (0.02)	
CF	Normal	48767 (99.99)	4033 (99.98)	0.328**
	Diagnosed	4 (0.01)	1 (0.02)	
CAH	Normal	34288 (99.98)	2893 (99.97)	0.433**
	Diagnosed	6 (0.02)	1 (0.03)	
SMA	Normal	14692 (99.99)	1299 (99.92)	0.156**
	Diagnosed	1 (0.01)	1 (0.08)	

PKU: Phenylketonuria, CH: Congenital hypothyroidism, BD: Biotinidase deficiency, CF: Cystic fibrosis, CAH: Congenital adrenal hyperplasia, SMA: Spinal muscular atrophy

DISCUSSION

Although newborn screening programs hold a significant place as a secondary prevention practice, studies examining the incidence of diseases within these programs are crucial for determining the frequency of these diseases and identifying potential risk factors. A 2022 study in Diyarbakır reported an incidence of phenylketonuria at 1:7878.[5] In Kırşehir, the incidence was found to be 1:7924, while in Sivas, it was 1:1334.[3,7] Globally, incidences vary across different countries and regions (11). For instance, PKU incidences in Europe are 1:4000 in Italy, 1:4545 in Ireland, 1:13434 in Denmark, and 1:112000 in Finland. In Asia, examples include incidences of 1:5000 in Iran and Jordan, 1:14245 in Saudi Arabia, 1:227273 in Thailand, 1:125000 in Japan, and 1:116006 in the Philippines. In the United States, incidence rates vary between 1:15000 and 1:47000 across different studies.[1,12] In our study, the five-year incidence was found to be 1:2407. Turkey's national incidence stands at 1:4500. Generally, phenylketonuria, which is more frequent in Eastern societies, is often attributed to consanguineous marriages.[5] Compared to other studies within Turkiye, the incidence of phenylketonuria in Adıyaman appears to be higher. While the incidence of PKU, a genetic disease, is generally decreasing, there have been fluctuations in Adıyaman over the past five years. Despite the decline, which we attribute to the effectiveness of genetic counseling, the incidence in Adıyaman remains high. We believe this is due to the higher rate of consanguineous marriages compared to the rest of Turkiye.[13] However, prospective studies are recommended to investigate factors such as access to healthcare, particularly in rural areas, and barriers to obtaining genetic counseling.

Congenital hypothyroidism is the most common disease screened worldwide.[3] A study conducted in Kırşehir found a six-year incidence of 1:1132, while a ten-year

incidence of 1:378 was reported in Sivas.[3,7] Incidences of 1:7175 and 1:2000 have been reported in Saudi Arabia and Japan, respectively.[1,14] In our study, the incidence was calculated at 1:1582. Hypothyroidism, a common disease both globally and in Turkiye, is thought to be influenced by preterm births and diet.[14]

A study in Diyarbakır that examined ten years of data found an incidence of biotinidase deficiency at 1:2359.[5] In Kırşehir, the annual incidence, based on six years of data, was reported as 1:2264, while in Sivas, the annual incidence, based on five years of data, was 1:3255.[3,7] Studies conducted in Şanlıurfa and Adana reported incidences of 1:1195 and 1:1177, respectively.[15,16] A study in Saudi Arabia covering six years of data found an incidence of 1:28316.[17] In Turkiye, 1637 newborns were diagnosed with biotinidase deficiency in 2021. According to TÜİK data, the incidence for 2021 was calculated as 1:660 when divided by the number of live births in the same year.[10,18] Two studies in Italy reported biotinidase deficiency incidences of approximately 1:6000.[19,20] In our study, the five-year annual incidence was found to be 1:481. The incidence of biotinidase deficiency can vary in different studies. This variation could be due to the different sample sizes and the timing of the studies, but the high incidence in Adıyaman is noteworthy. As with PKU, consanguineous marriages are considered a factor in biotinidase deficiency, but conducting further studies would be beneficial to better understand the specific increase in its incidence.

A study in Mersin on cystic fibrosis, analyzing three years of data, found an annual incidence of 1:9388.[21] A study in Kırşehir examining data from 2015 to 2020 found no cases of cystic fibrosis diagnosed.[7] When examining Turkey's 2021 data, the annual incidence was calculated at 1:8570.[10,18] While the global incidence of CF is thought to be 1:2500, screening programs have shown a declining trend in this ratio. Incidence studies in Europe have reported 1:1353 in Ireland, 1:25000 in Finland, 1:4500 in Western Europe, and around 1:6000 in Northern Europe.[21] In other parts of the world, incidences have been reported as 1:3000 in Australia, 1:3300 in Canada, and 1:4000 in the United States.[22] In our study, the incidence of CF was calculated as 1:10593. The data appear consistent with those from other cities in Turkiye and the country's incidence.

Congenital Adrenal Hyperplasia (CAH) was included in the national program in 2022 but was already being screened in pilot provinces like Adıyaman and Sivas. In Sivas, examining 2020 and 2021 data, the incidence was calculated at 1:4420.[3] For 2021, the annual incidence in Turkiye was calculated at 1:10383.[10,18] An analysis of eight years of data in Saudi Arabia reported an incidence of 1:7908.[1] In the United States, a 15-year study found an incidence of 1:13493.[23] In India, a 2019 study reported an incidence of 1:2500.[24] In Denmark, a ten-year data review found an incidence of 1:20000.[25] Globally, the incidence of CAH is estimated to range between 1:10000 and 1:20000.[26] In our study, the incidence of CAH was calculated as 1:5864. Studies investigating the incidence of CAH in different regions of Turkiye are scarce, likely due to the recent inclusion of the disease in the screening program. Although a study conducted in the province of Sivas found a low incidence, it would not be entirely accurate to state that CAH is more common in Adıyaman based on a comparison with just one province. However, considering global studies, the influence of consanguineous marriages in Adıyaman, where certain diseases are generally more prevalent, cannot be overlooked. Further research is recommended to explore consanguineous marriages and other potential risk factors.

Spinal muscular atrophy (SMA) screening began nationwide in Turkiye in 2022. The annual incidence for 2022 in Turkiye was calculated at 1:9590.[10,27] A study in the United States examining three years of data found an incidence of 1:19000.[28] A study in Japan reviewing nine years of data found an incidence of 1:100000.[29] However, a study in Germany reported an incidence of 1:6910 among 297163 newborns, with 43 diagnosed with SMA.[30] In our study, examining two years of data, the incidence was 1:9489. The incidence in Adıyaman is consistent with that of Turkiye. However, global studies show a wide range of incidence intervals, indicating the need for more studies on this topic.

Limitations

Due to the study's retrospective nature and the lack of additional information requested from families, it was impossible to establish causal relationships. No statistically significant risk factors were identified when examining the available demographic data. The study's results may not be generalizable since it was conducted only in Adıyaman province. However, the study shows that Turkiye generally screens fewer diseases than developed countries and detects higher incidences of the diseases screened. Additionally, the study has been identified as the first in Turkiye to screen for six diseases, including SMA.

CONCLUSION

In our study, we found that newborns in Adıyaman were generally diagnosed with diseases screened in the National Newborn Screening Program at a higher frequency than the Turkish average. However, biotinidase deficiency, in particular, was slightly more prevalent. Further studies should be planned to investigate the frequency of biotinidase deficiency, specifically in Adıyaman, and

efforts should be made to raise social awareness in Turkey about reducing consanguineous marriages, which is a potential cause.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethical approval for the study was obtained from the Non-interventional Researches Ethics Committee of Fırat University (Date: 14.12.2023, Decision No: 2023-14/32).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All the authors declare that they have all participated in the design, execution, and analysis of the study and that they have approved the final version.

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