DOI: 10.4274/jcrpe.galenos.2026.2025-10-12

Case Report

Striking Scrotal Hyperpigmentation as an Early Clinical Sign of Familial Glucocorticoid Deficiency Type 2: A Case with Homozygous *MRAP* Variant

Gözde Gürpınar[1], Duygu Gamze Aracı[2], Yakup Karakurt[3]
[1]University of Health Sciences Türkiye, Bağcılar Training and Research Hospital, Department of Pediatrics, Division of Pediatric Endocrinology, İstanbul, Türkiye
[2]University of Health Sciences Türkiye, Bağcılar Training and Research Hospital, Department of Medical Genetics, İstanbul, Türkiye
[3]University of Health Sciences Türkiye, Bağcılar Training and Research Hospital, Department of Pediatrics, Division of Neonatology, İstanbul, Türkiye

Abstract
Familial glucocorticoid deficiency type 2 (FGD2) is a rare autosomal recessive disorder caused by pathogenic variants in the *MRAP* gene, typically characterized by isolated cortisol deficiency with markedly elevated ACTH levels. We report a term male neonate born to consanguineous parents who presented with striking scrotal hyperpigmentation at birth, despite an otherwise normal appearance and a normal newborn screening limited to classical congenital adrenal hyperplasia (CAH). Initial biochemical evaluations, including glucose and electrolytes, were unremarkable; however, due to severe hyperpigmentation, further endocrine workup was pursued. Laboratory findings revealed profoundly low serum cortisol and markedly elevated ACTH, supporting the diagnosis of primary adrenal insufficiency**.** Hydrocortisone therapy was initiated promptly, and during follow-up, transient hyperkalemia and low-normal aldosterone levels necessitated short-term fludrocortisone supplementation, suggesting partial mineralocorticoid involvement. Genetic analysis identified a homozygous MRAP in-frame deletion (c.88_90del; p.K30del), classified as likely pathogenic according to ACMG 2015 criteria and as a variant of uncertain significance according to the ClinGen SVI recommendations. Despite the dramatic initial presentation, the patient remained euglycemic and demonstrated normal neurodevelopment under appropriate hormone replacement, with gradual resolution of hyperpigmentation. This case highlights striking neonatal scrotal hyperpigmentation as a potential early clinical clue suggestive of familial glucocorticoid deficiency in a patient with a homozygous *MRAP* variant. Importantly, even when newborn screening for CAH is normal, marked hyperpigmentation should prompt evaluation for other causes of primary adrenal insufficiency to prevent life-threatening adrenal crises.
Keywords: Familial glucocorticoid deficiency, MRAP mutation, neonatal hyperpigmentation

What is already known on this topic?
FGD2 is classically described as isolated glucocorticoid deficiency due to *MRAP* mutations, presenting in infancy or early childhood with generalized hyperpigmentation, hypoglycemia, and recurrent infections. Newborn screening typically does not detect non-CAH causes of primary adrenal insufficiency.

What this study adds?
This report describes an atypical neonatal presentation of FGD2 with striking scrotal hyperpigmentation despite normal CAH screening, emphasizing that adrenal insufficiency may exist without overt metabolic crises. These findings highlight the importance of considering alternative causes of primary adrenal insufficiency and performing comprehensive hormonal and genetic evaluation when marked hyperpigmentation is present.

Dr. Gözde Gürpınar, University of Health Sciences Türkiye, Bağcılar Training and Research Hospital, Department of Pediatrics, Division of Pediatric Endocrinology, İstanbul, Türkiye
drgozdegurpinar@gmail.com
0000-0001-8623-5270

15.10.2025
13.07.2026

Epub: 22.07.2026

Introduction
Primary adrenal insufficiency (PAI) results from impaired adrenal cortical function, leading to reduced cortisol secretion (1). Inherited forms of PAI arise from two main categories of disorders: congenital adrenal hyperplasia (CAH) and non-CAH etiologies (1–4).
Newborn screening (NBS) significantly reduces mortality in congenital adrenal hyperplasia (CAH), particularly in the salt-wasting form caused by 21-hydroxylase deficiency. Nevertheless, newborn screening programs are primarily designed to detect CAH, and non-CAH primary adrenal insufficiency (PAI) may remain undiagnosed. The definitive diagnosis of non-CAH primary adrenal insufficiency can be guided by assessing which steroid pathway is affected (mineralocorticoids, glucocorticoids, or androgens), the age at presentation, and the presence of associated clinical features. Genetic analysis is playing an increasingly important role in reaching a specific diagnosis. Several genes have been implicated in the etiology of non-CAH PAI cases, including homozygous or compound heterozygous inactivating mutations of *MC2R, MRAP, CYP11A1, STAR, NR5A1, AAAS, NNT, SGPL1, AIRE, TXNRD2, MCM4,* and *POLE1;* or heterozygous activating mutations of SAMD9 and *CDKN1C. NR0B1/DAX1* and *ABCD1* mutations are inherited in an X-linked manner in the great majority of cases (5-10). In 2005, Metherell et al. conducted autozygosity mapping in a single family in which runs of homozygosity identified a 2.2 Mbp region. Although *MC2R* loss-of-function mutations were first identified as the primary cause of familial glucocorticoid deficiency (FGD), the presence of families with adrenal insufficiency and negative *MC2R* screening suggested additional genetic factors. Noon et al. demonstrated that *MC2R* requires an adrenal-specific co-factor for proper trafficking to the cell surface, as expression was restricted to the endoplasmic reticulum in non-adrenal cells. Within this region, the adrenally expressed chromosome 21 open reading frame 61 (C21orf61) gene previously encoding a fat- associated low-molecular-weight protein, was identified (11). Variants in this gene, retitled the melanocortin 2 receptor accessory protein (MRAP), were subsequently identified in several families with FGD. Variants in *MRAP* (FGD Type 2) account for 20-25% of FGD cases, with around 15 mutations being described since initial characterisation of this gene (11–14).

In the present paper, we describe a patient who was born with severe scrotal hyperpigmentation, had normal newborn screening results, and was subsequently found to carry a homozygous variant in the *MRAP* gene.

Case

A male infant was referred to our clinic immediately after birth with marked scrotal hyperpigmentation. The patient was born in Turkey to consanguineous parents of Syrian origin (fourth-degree relatives). The patient was the first surviving male child of a G5P3A2 mother, with two previous spontaneous miscarriages at approximately 6 weeks of gestation that were reported as anembryonic pregnancies**.** He was delivered at 39+6 weeks of gestation via spontaneous vaginal delivery following an uneventful pregnancy. At birth, his anthropometric measurements were as follows: weight 3580 g (50–75th percentile), length 51 cm (50–75th percentile), and head circumference 35 cm (50–75th percentile). On physical examination, the external genitalia showed a penis of normal length and bilaterally descended testes; however, there was striking hyperpigmentation of the scrotal skin. Mild hyperpigmentation was also observed in other typical areas such as the palmar creases and knuckles, but the scrotal pigmentation was disproportionately severe and represented the most prominent clinical finding. Dysmorphic features included hypertelorism, almond-shaped eyes, frontotemporal hypertrichosis, wide nasal bridge and a thin upper lip. Written informed consent for publication of the clinical data and photographs was obtained from the patient's mother.

Blood chemistry results were within the normal neonatal range: glucose 79 mg/dL (45–90), sodium 137 mmol/L (135–145), potassium 5.63 mmol/L (3.5–5.9), chloride 109 mmol/L (98–110), ALT 28 IU/L (10–40), and AST 30 IU/L (30–150). Total blood count was normal. Blood gas analysis was within normal limits. There was no history of vomiting. The adrenal axis evaluation had not yet been completed. As the overall clinical condition was stable, the patient was discharged home with the mother, but was scheduled for an early outpatient follow-up visit. At the follow-up visit on day 4 of life, the patient's hormonal evaluation had been completed. Serum hormone analyses showed the following: cortisol 4 µg/dL (2.8–23), ACTH 1089 pg/mL (6–48), plasma renin activity (PRA) 9.08 ng/mL/h (2.35–37), aldosterone 14.4 ng/dL (17–154), DHEA-S 640.7 µg/dL (88–356), and androstenedione 0.59 ng/mL (0.2–2.9), 17-hydroxyprogesterone 0.01 ng/mL (0.03-0.09 ng/ml), glucose: 71 mg/dL, Na: 135 mmol/L, K: 6.6 mmol/L. Abdominal ultrasonography demonstrated normal adrenal glands and no structural abnormalities in the liver, spleen, kidneys, or other abdominal organs. Cranial ultrasonography revealed normal brain parenchyma and ventricular system. Based on these findings, the patient was diagnosed with non-CAH PAI and during the acute phase, intravenous hydrocortisone was administered as a continuous infusion (100 mg/m²/day), followed by maintenance therapy given in three divided doses (10 mg/m²/day) with the largest dose in the morning. Although haemolysis was initially considered as a possible cause of the elevated potassium level, repeat measurements confirmed persistent hyperkalemia. As shown in Table 1, serum potassium increased to 7.92 mmol/L on day 10 of life. Aldosterone levels were within the low range, and plasma renin activity was 9.41 ng/mL/h (reference range: 2.35–37 ng/mL/h). Given the severity of hyperkalemia and the ongoing suspicion of primary adrenal insufficiency, fludrocortisone therapy was initiated at a dose of 0.05 mg/day on day 10 of life. Following normalization of serum potassium levels and suppression of plasma renin activity, fludrocortisone therapy was gradually tapered and discontinued at two months of age, suggesting that mineralocorticoid replacement was required only transiently during the neonatal period. The markedly elevated DHEA-S level observed in the neonatal period likely reflects physiological secretion from the fetal adrenal zone, which is prominent at birth and declines rapidly during early infancy. Consistent with this pattern, DHEA-S levels decreased markedly during follow-up. The newborn screening test result was reported as normal at 15 days of age. Genetic analysis identified a homozygous c.88_90del variant in the *MRAP* gene.

On his most recent visit, at the age of 6 months, there was a significant regression of hyperpigmentation (Figure 1). His height was 66 cm (42^{nd} percentile), weight 8.4 kg (78^{th} percentile). The patient's scrotal hyperpigmentation improved during follow-up. His neurodevelopment was appropriate for age. The ACTH level was normal by 10 mg/m^2/d oral hydrocortisone treatment.

Genomic DNA analysis

Informed consent for the molecular studies was obtained from all family members. Genomic DNA was extracted from peripheral blood samples using the QIAamp DNA Mini Kit (Qiagen, Germany). The index patient's genomic DNA was captured using the Clinical Exome Solution v3 (Sophia Genetics) targeting 6,380 genes. The libraries were sequenced on the Illumina NextSeq 500 platform. The Sophia DDM platform was used for bioinformatics analysis. CNV (copy number variant) analysis was performed using MUSKAT algorithm from NGS-derived read-depth data.

In the variant prioritization step, a phenotype-driven filtering strategy was applied using Human Phenotype Ontology (HPO) terms relevant to the patient's clinical presentation, including adrenal insufficiency (HP:0000846) and scrotal hyperpigmentation (HP:0012855). Genes associated with these phenotypes were specifically evaluated. During variant filtering, low-quality variants and common variants with a minor allele frequency greater than 1% in population databases (e.g., gnomAD) were excluded. In addition, variants located in intronic regions beyond ±20 base pairs from exon–intron boundaries were filtered out. Synonymous variants without predicted splice effects were also removed. After this filtering process, the remaining variants were evaluated for their predicted functional impact and clinical relevance.A homozygous in-frame deletion (c.88_90del) in exon 1 of the *MRAP* gene (NM_001379228) was identified. This variant removes a single lysine residue at codon 30 (p.Lys30del, p.K30del). Segregation analysis within the family showed that both parents and one unaffected sibling were heterozygous carriers of the variant. Genetic testing could not be performed for the other unaffected sibling. No other pathogenic or likely pathogenic variants associated with primary adrenal insufficiency were identified in the analyzed gene set.

This variant is exceedingly rare in population databases (gnomAD v4.1.0: 1/1,613,936 alleles; no homozygous). p.K30del variant has been previously reported in patients with glucocorticoid deficiency in the literature (5,15). However, no functional studies have yet been performed on this variant.

According to the American College of Medical Genetics and Genomics and the Association for Molecular Pathology (ACMG/AMP) 2015 guidelines (17), the variant meets the criteria **PM2, PM3, and PM4**, which would support a classification of **likely pathogenic**. However, when interpreted according to the updated recommendations of the ClinGen Sequence Variant Interpretation (SVI) Working Group (16), the variant is categorized as a **Variant of Uncertain Significance (VUS)(PM2_P, PM3 and PM4)**.

Discussion

FGD usually presents in infancy or in early childhood with hyperpigmentation, failure to thrive, recurrent infections, hypoglycemic attacks and convulsions that may result in coma or death (10). We report a case of familial glucocorticoid deficiency 2 (FGD) with a homozygous *MRAP* mutation in a neonate. The patient presented with striking scrotal hyperpigmentation, low serum cortisol levels, and markedly elevated ACTH concentrations, while serum electrolytes remained within the normal range. Severe cutaneous hyperpigmentation in FGD results from overstimulation of melanocortin-1 receptors (MC1R) by high circulating levels of melanocyte-stimulating hormone (MSH), a cleavage product of ACTH derived from proopiomelanocortin (18). Following initiation of glucocorticoid therapy, ACTH concentrations decline and the hyperpigmentation typically regresses (19). In our case, the patient exhibited marked hyperpigmentation at birth, suggesting that fetal corticotrophs may secrete excessive ACTH in response to reduced fetal cortisol, which subsequently activates melanocytes and enhances pigmentation.

Previous reports from Turkey describe patients diagnosed later in infancy after presenting with recurrent hypoglycemia or convulsions (20), whereas our patient was recognized in the neonatal period due to prominent hyperpigmentation. In another case involving a different MRAP gene variant, the patient presented on the first postnatal day with diffuse hyperpigmentation and hypoglycemia. By contrast, our patient exhibited diffuse hyperpigmentation with particularly prominent scrotal involvement but remained euglycemic throughout the follow-up period, suggesting possible phenotypic variability among MRAP-related adrenal disorders (21).

Patients with FGD often have undetectable levels of adrenal androgens (22). In our patient, serum 17-hydroxyprogesterone and androstenedione levels were within the age-appropriate reference range. The markedly elevated DHEA-S level observed in the neonatal period likely reflects physiological secretion from the fetal adrenal zone, which is prominent at birth and declines rapidly during early infancy. Consistent with this physiological pattern, DHEA-S levels decreased during follow-up.

Our findings highlight the importance of considering rare non-CAH etiologies in neonates presenting with severe adrenal insufficiency despite a normal CAH newborn screen, to prevent diagnostic delay and ensure timely treatment. In Turkey, nationwide newborn screening for congenital adrenal hyperplasia (CAH) was implemented in early 2022 (23). The Turkish Directorate of Public Health adopted a one-sample, two-tier protocol. First-tier screening measures 17-hydroxyprogesterone (17-OHP) in dried blood spots, and samples with elevated levels are reanalyzed by LC–MS/MS for steroid profiling, enabling detection of both classic and rare CAH forms. In our patient, the newborn screening result was reported as normal.

In our patient, serum potassium levels were elevated, while aldosterone levels were low and plasma renin activity remained within the normal range. Given the severity of hyperkalemia and the ongoing suspicion of primary adrenal insufficiency, mineralocorticoid replacement with fludrocortisone was initiated. Although familial glucocorticoid deficiency (FGD) is classically characterized by isolated glucocorticoid deficiency with preserved mineralocorticoid function, our case demonstrated a transient requirement for mineralocorticoid replacement during the neonatal period.

Under normal physiological conditions, angiotensin II is the principal regulator of mineralocorticoid synthesis. However, the ACTH receptor (MC2R) is also expressed in the zona glomerulosa, and administration of synthetic ACTH has been shown to induce a rapid, dose-dependent increase in aldosterone secretion (24–27). This suggests that ACTH plays a facilitatory role in mineralocorticoid production, supported by experimental evidence demonstrating that the CYP11B2 promoter is cAMP responsive.

In this context, impaired ACTH signaling due to MRAP dysfunction may contribute to transient disturbances in mineralocorticoid regulation, particularly during early infancy—a period characterized by relative mineralocorticoid insensitivity. Therefore, in ACTH-resistant states, mild alterations in renin–sodium homeostasis may be observed (27).

Guran et al. (2016) reported that two of nine patients with *MRAP* variants required mineralocorticoid replacement, suggesting that partial mineralocorticoid deficiency may occasionally accompany glucocorticoid deficiency in this genetic form of primary adrenal insufficiency (5).

In a recent single-center cohort study from India, Daga et al. reported that approximately two-thirds of pediatric patients with non-CAH primary adrenal insufficiency had mineralocorticoid deficiency, and notably, this subgroup included a patient carrying an *MRAP* mutation (28).

Although approximately 10–15% of individuals with ACTH resistance as part of Triple A (Allgrove) syndrome show evidence of mineralocorticoid deficiency, disturbances in renin–sodium homeostasis have not been well established in other ACTH-resistance syndromes such as FGD1 or FGD2. Accordingly, prior to confirmation of the genetic diagnosis, Triple A syndrome was considered in the differential diagnosis due to the need for mineralocorticoid replacement; however, the absence of alacrima and achalasia made this diagnosis less likely.

More broadly, primary adrenal insufficiency in infancy may result from both genetic and acquired conditions, and careful evaluation of the differential diagnosis is essential. In our patient, acquired causes such as adrenal hemorrhage, trauma, or infection were excluded based on clinical history and laboratory findings. Congenital adrenal hyperplasia was considered unlikely due to normal 17-hydroxyprogesterone levels. Clinical exome sequencing did not identify pathogenic variants in other genes known to be associated with primary adrenal insufficiency, and X-linked adrenal hypoplasia congenita was also excluded as no pathogenic variants were detected in the NR0B1 (DAX1) gene. Taken together, these findings support the diagnosis of familial glucocorticoid deficiency associated with an MRAP variant.

These findings suggest that although familial glucocorticoid deficiency due to *MRAP* variants is typically characterized by preserved mineralocorticoid function, exceptions may occur, highlighting the importance of careful biochemical evaluation in affected patients. While hyponatremia was reported to be more common than hyperkalemia in previous studies , hyperkalemia was more pronounced in our case.

In conclusion**,** the only disease that a negative neonatal CAH screening reliably excludes is classical 21-hydroxylase deficiency. Nevertheless, neonates may still present with other rare forms of CAH, non-CAH primary adrenal insufficiency, or central adrenal insufficiency. Adrenal dysfunction should be considered in any symptomatic newborn, even if the screening result, biochemical parameters, and glucose levels are initially normal. Importantly, scrotal or generalized hyperpigmentation should not be overlooked, as it may be an early clue to adrenal insufficiency.

References

1. Husebye ES, Pearce SH, Krone NP, Kämpe O. Adrenal insufficiency. Lancet. 2021;397:613-629. doi:10.1016/S0140-6736(21)00136-7.
2. Buonocore F, Achermann JC. Primary adrenal insufficiency: New genetic causes and their long-term consequences. Clin Endocrinol (Oxf). 2020;92:11-20. doi:10.1111/cen.14109.
3. Kirkgoz T, Guran T. Primary adrenal insufficiency in children: Diagnosis and management. Best Pract Res Clin Endocrinol Metab. 2018;32:397-424. doi:10.1016/j.beem.2018.05.010.
4. Malikova J, Flück CE. Novel insight into etiology, diagnosis and management of primary adrenal insufficiency. Horm Res Paediatr. 2014;82:145-157. doi:10.1159/000363107.
5. Guran T, Buonocore F, Saka N, Ozbek MN, Aycan Z, Bereket A, et al. Rare causes of primary adrenal insufficiency: Genetic and clinical characterization of a large nationwide cohort. J Clin Endocrinol Metab.2016;101:284-292. doi:10.1210/jc.2015-3250.
6. Buonocore F, Maharaj A, Qamar Y, Bizzarri C, Benevento D, Baronio F, et al. Genetic analysis of pediatric primary adrenal insufficiency of unknown etiologies: 25 years' experience in the UK. J Endocr Soc. 2021;5:bvab086. doi:10.1210/jendso/bvab086.
7. Capalbo D, Moracas C, Cappa M, Bizzarri C, De Luca F, Matarazzo P, et al. Primary adrenal insufficiency in childhood: Data from a large nationwide cohort. J Clin Endocrinol Metab. 2021;106:762-773. doi:10.1210/clinem/dgaa881.
8. Wijaya M, Huamei M, Jun Z, Zhiyong Z, Xiaoping L, Li L, et al. Etiology of primary adrenal insufficiency in children: A 29-year single-center experience. J Pediatr Endocrinol Metab. 2019;32:615-622. doi:10.1515/jpem-2018-0445.
9. Amano N, Narumi S, Hayashi M, Takagi M, Igarashi M, Hasegawa T, et al. Genetic defects in pediatric-onset adrenal insufficiency in Japan. Eur J Endocrinol. 2017;177:187-194. doi:10.1530/EJE-17-0027.
10. Perry R, Kecha O, Paquette J, Huot C, Van Vliet G, Deal C. Primary adrenal insufficiency in children: Twenty years' experience at the Sainte-Justine Hospital, Montreal. J Clin Endocrinol Metab. 2005;90:3243-3250. doi:10.1210/jc.2004-0016.
11. Metherell LA, Chapple JP, Cooray SN, David A, Becker C, Ruschendorf F, et al. Mutations in MRAP, encoding a new interacting partner of the ACTH receptor, cause familial glucocorticoid deficiency type 2. Nat Genet.2005;37:166-170. doi:10.1038/ng1501.
12. Chen C, Zhou R, Fang Y, Jiang L, Liang L, Wang C. Neonatal presentation of familial glucocorticoid deficiency with a MRAP mutation: A case report. Mol Genet Metab Rep. 2016;9:15-17. doi:10.1016/j.ymgmr.2016.09.003.
13. Smith C, Maharaj AV, Qamar Y, Read J, Williams J, Chan L, et al. In vitro splicing assay proves the pathogenicity of intronic variants in MRAP. J Endocr Soc. 2021;5(Suppl 1):A85-A86. doi:10.1210/jendso/bvab048.172.

14. Modan-Moses D, Ben-Zeev B, Hoffmann C, Falik-Zaccai TC, Bental YA, Pinhas-Hamiel O, et al. Unusual presentation of familial glucocorticoid deficiency with a novel MRAP mutation. J Clin Endocrinol Metab.2006;91:3713-3717. doi:10.1210/jc.2006-0687.
15. Bideci A, Doğer E, Akbaş E, Uğurlu M, et al. Familial glucocorticoid deficiency type 2: A new mutation in the MRAP gene (p.K30del). Horm Res Paediatr. 2017.
16. ClinGen Sequence Variant Interpretation Working Group. ClinGen sequence variant interpretation recommendation for PM2 (Version 1.0). Available from: https://clinicalgenome.org.
17. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants. Genet Med. 2015;17:405-424. doi:10.1038/gim.2015.30.
18. Rousseau K, Kauser S, Pritchard LE, Warhurst A, Oliver RL, Slominski A, et al. Proopiomelanocortin is secreted by keratinocytes and melanocytes and stimulates melanogenesis. FASEB J. 2007;21:1844-1856. doi:10.1096/fj.06-7398com.
19. Ramachandran P, Penhoat A, Naville D, Begeot M, Abdel-Wareth LO, Sedaghatian MR. Familial glucocorticoid deficiency type 2 in two neonates. J Perinatol. 2003;23:62-66. doi:10.1038/sj.jp.7210813.
20. Akın L, Kurtoğlu S, Kendirci M, Akın MA. Familial glucocorticoid deficiency type 2: A case report. J Clin Res Pediatr Endocrinol. 2010;2:122-125. doi:10.4274/jcrpe.v2i3.122.
21. Kurt I, Eser M, Kahveci A, et al. Severe adrenal insufficiency in six neonates with normal newborn screening for CAH. Clin Endocrinol (Oxf). 2024;101:108-113. doi:10.1111/cen.15080.
22. Weber A, Clark AJ, Perry LA, Honour JW, Savage MO. Diminished adrenal androgen secretion in familial glucocorticoid deficiency. Clin Endocrinol (Oxf). 1997;46:431-437. doi:10.1046/j.1365-2265.1997.1580969.x.
23. Güran T, Tezel B, Gürbüz F, Selver Eklioğlu B, Hatipoğlu N, Kara C, et al. Neonatal screening for congenital adrenal hyperplasia in Turkey. J Clin Res Pediatr Endocrinol. 2019;11:13-23. doi:10.4274/jcrpe.galenos.2018.2018.0117.
24. Xia Y, Wikberg JE. Localization of ACTH receptor mRNA in mouse adrenal gland. Cell Tissue Res. 1996;286:63-68. doi:10.1007/s004410050675.
25. Reincke M, Beuschlein F, Menig G, Hofmockel G, Arlt W, Lehmann R, et al. ACTH receptor expression in adrenal cortex. J Endocrinol. 1998;156:415-423. doi:10.1677/joe.0.1560415.
26. Arvat E, Di Vito L, Lanfranco F, et al. ACTH effects on cortisol, aldosterone and DHEA secretion. J Clin Endocrinol Metab. 2000;85:3141-3146.
27. Lin L, Hindmarsh PC, Metherell LA, Alzyoud M, Al-Ali M, Brain CE, et al. ACTH receptor mutations in adrenal hypoplasia. Clin Endocrinol (Oxf). 2007;66:205-210. doi:10.1111/j.1365-2265.2006.02709.x.
28. Daga A, Karlekar M, Lila A, Sarathi V, Sharma A, Memon SS, et al. Non-CAH pediatric primary adrenal insufficiency: A single-center experience. J Pediatr Endocrinol Metab. 2025;38:383-390. doi:10.1515/jpem-2024-0476.

Table 1. Hormonal and biochemical parameters of the patient during follow-up

Date	ACTH (pg/mL)	Cortisol (µg/dL)	Aldosterone (ng/dL)	PRA (ng/mL/h)	Potassium (mmol/L)	Sodium (mmol/L)	Glucose (mg/dl)	DHEA-S (µg/dL)	Androstenedione (ng/mL)	Treatment
Initial presentation (Day 1)					5.63	137	79			
Day 4 of life	1089	4	14.4	9.08	6.60	135	81	640.7	0.59	HC started
Day 10 of life	558	11	6.9	9.41	7.92	137	85			HC + FC started
1st month	8.94	5.07	26.2	8.46	6.13	137	88	6.6	<0.30	HC + FC
2nd month	6.1	10.64	5.8	0.15	4.13	138	90			HC
6th month	4.4	17.07	24.6	14.59	5.78	137	94	<1.5	<0.30	HC

Abbreviations: ACTH, adrenocorticotropic hormone; PRA, plasma renin activity; HC, hydrocortisone; FC, fludrocortisone. **Reference ranges:** ACTH: 6–48 pg/mL; cortisol: 2.8–23 µg/dL; aldosterone: 17–154 ng/dL (1–30 days) and 6.5–86 ng/dL (1–12 months); plasma renin activity: 2.35–37 ng/mL/h; potassium: 3.5–5.9 mmol/L; sodium: 135–145 mmol/L; glucose: 45–90 mg/dL; DHEA-S: 88–356 µg/dL; androstenedione: 0.2–2.9 ng/mL (1–7 days) and 0.68–2.36 ng/mL (1–12 months).

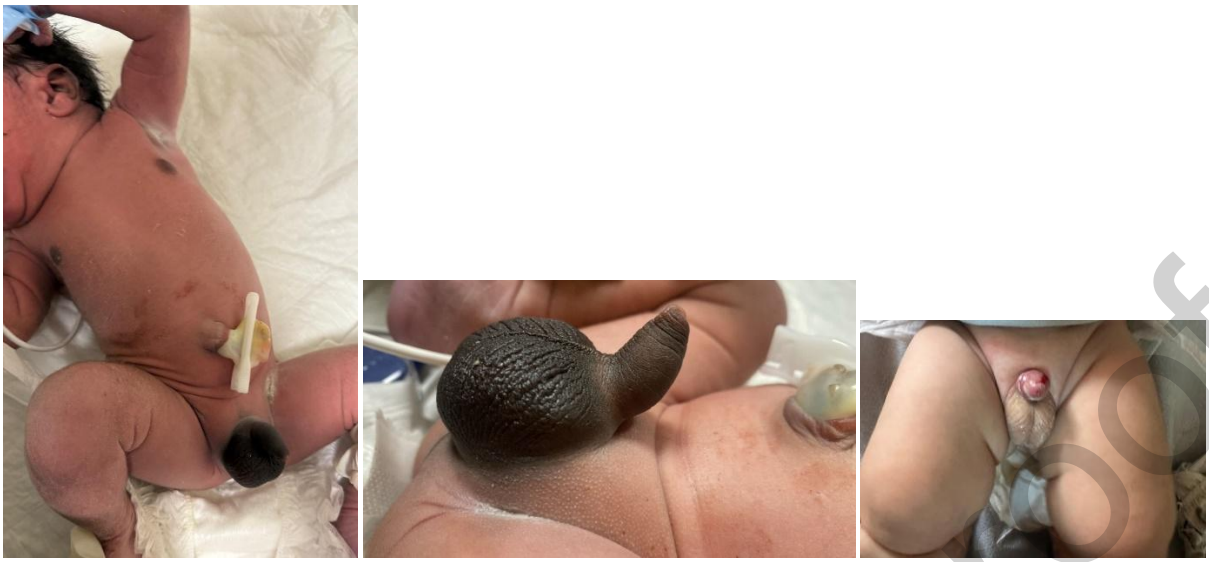

Figure 1. Clinical appearance of scrotal hyperpigmentation before treatment and after treatment at 6 months of age, demonstrating marked regression of pigmentation following glucocorticoid therapy.