CASE REPORT

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Xp21 Contiguous Gene Deletion Syndrome: Diagnosis, Treatment, and a Review of the Literature on a Rare Genetic Disorder

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What is already known on this topic?

Complex glycerol kinase deficiency (CGKD) usually arises from a partial deletion of the Xp21 chromosomal region, affecting genes associated with GKD, adrenal hypoplasia, Duchenne muscular dystrophy, and other conditions that lead to various developmental abnormalities. Symptoms are related to the size of the deletion and may manifest in early life.

What this study adds?

CGKD is an uncommon condition and this report describes our experiences with a patient diagnosed with CGKD. This case highlights the rare yet significant clinical and genetic diversity linked to Xp21 contiguous gene deletion syndrome and it is hoped that this case report will enhance the recognition and clinical management of these patients.

ABSTRACT

Xp21 contiguous gene deletion syndrome is an uncommon genetic condition associated with complex glycerol kinase deficiency (*GK*), congenital adrenal hypoplasia (*NR0B1*), Duchenne muscular dystrophy (*DMD*), and, in some cases, intellectual disability. Clinical findings vary based on the

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size of the deletion and the number of affected genes. To date, over 100 male patients with this syndrome have been reported, while the number of symptomatic female carriers is quite limited. In this article, we present the diagnosis and treatment process of a case exhibiting dysmorphic facial features, signs of adrenal insufficiency, pseudo-hypertriglyceridemia, and elevated creatine phosphokinase levels. The patient's serum 17-hydroxyprogesterone levels were normal, and the adrenal glands were not observable via magnetic resonance imaging. An Xp21.2 deletion (*DMD, NR0B1, GK, IL1RAPL1*) was identified in the case. Treatment with hydrocortisone, fludrocortisone, and oral salt was arranged. This case highlights the rare yet significant clinical and genetic diversity of Xp21 contiguous gene deletion syndrome.

Keywords: Complex glycerol kinase deficiency, congenital adrenal hypoplasia, Duchenne muscular dystrophy, glycerol kinase deficiency, pseudo-hypertriglyceridemia

Introduction

Xp21 contiguous gene deletion syndrome is a rare genetic metabolic disorder that arises from the deletion of a chromosomal segment encompassing the glycerol kinase (GK) locus in the Xp21 region (1). The genetic loci for adrenal hypoplasia (AHC), Duchenne muscular dystrophy (DMD), chronic granulomatous disease (CGD), ornithine transcarbamylase (OTC) deficiency, and retinitis pigmentosa (RP) are frequently involved. The loci for AHC and DMD are located near the glycerol kinase deficiency (GKD) locus, which makes the combination of AHC, GKD, and DMD the most common genotype in this condition, referred to as complex glycerol kinase deficiency (CGKD) (2).

The symptoms depend on the extent of the deletion and may appear early in life. Diagnosis relies on clinical observations and laboratory results. Genetic testing can confirm the diagnosis by detecting a deletion at the Xp21 locus, and carrier status can be identified in female relatives (1,3).

This article presents a male infant with a complex phenotype of Xp21 contiguous gene deletion syndrome, featuring pseudo-hypertriglyceridemia, adrenal insufficiency (hyponatremia, hyperkalemia, dehydration), and increased creatine phosphokinase (CPK) levels, suggestive of DMD. Biochemical, cytogenetic, and molecular tests were performed to identify and assess the extent of the genomic deletion. Early diagnosis of CGKD gives the patient the possibility of optimal multi-profile medical care, which has a positive effect on the optimal individual development and the quality of life. This article highlights the diversity of the clinical course of the disease. We hope it will prove to be of help to other endocrinologists, to the benefit of our patients.

Case Report

An 8-month-and-13-day-old male was referred to our hospital due to respiratory distress, dehydration, and hypoglycemia. The patient had been diagnosed with adrenal insufficiency during the neonatal period and had been started on hydrocortisone, fludrocortisone, oral salt, and anti-potassium treatments. The patient had been receiving hydrocortisone treatment at approximately 8 mg/m²/day after the neonatal period, but the dose of hydrocortisone was likely not increased after an infection. Due to his poor general condition, he was admitted to the pediatric intensive care unit for monitoring.

The patient was born at 39 weeks, weighing 2900 grams and measuring 48 cm, via NSD from a 22-year-old mother. There was a first-degree consanguinity (sibling) between the parents, and the mother had a history of mental retardation. On physical examination, the patient's weight was 5 kg (<3rd percentile), height was 64 cm (<3rd percentile), and head circumference was 39 cm (<3rd percentile). He appeared in poor general condition, hypotonic, microcephalic, and dehydrated, with dysmorphic facial features including upward-deviated eyes and low-set ears. The skin showed hyperpigmentation, particularly evident in the scrotum. On examination of the genitourinary system, the stretched penis measured 4 cm, and the testicles were not palpable bilaterally. Other system examinations were normal.

On routine laboratory tests, the following results were obtained: glucose: 191 mg/dL (74-106) (prior to dextrose treatment at an external center, it was 39 mg/dL), sodium: 129.1 mEq/L (136-145), potassium: 6.4 mEq/L (3.5-5.1), aspartate aminotransferase: 1081 U/L (0-34), alanine aminotransferase: 293 U/L (10-49). Additional testing showed blood urea nitrogen: 31 mg/dL (9-23), creatinine: 0.43 mg/dL (0.7-1.3), uric acid: 6.9 mg/dL (3.7-9.2), hemoglobin: 11.7 g/dL, leukocytes: 14.7 10^3/mm³, platelets: 131 10^3/mm³, C-reactive protein: 61.3 mg/L (0-5), lactate dehydrogenase: 2736 U/L (120-246), and myoglobin: 2416 (0-110) ng/mL. Based on these findings, adrenal cortical insufficiency was suspected. The treatment doses were adjusted with fluid and electrolyte therapy in appropriate doses, with hydrocortisone at 30 mg/m²/day and fludrocortisone at 0.1 mg/day. The adrenocorticotropic hormone (ACTH) level was 9.07 pg/mL (0-46), serum cortisol was 40.2 µg/dL (4.3-22.4), 17-hydroxyprogesterone (17-OHP) was 0.35 ng/mL (0.59-3.44), renin was <0.14 ng/mL/hour (0.06-4.69), and aldosterone was >20 ng/dL (0-19.9) (Table 1). However, these tests were performed after the patient started hydrocortisone and fludrocortisone treatments. During the diagnosis in the neonatal period, ACTH was found to be 612 pg/mL (0-46) and cortisol 0.8 µg/dL (4.3-22.4). Also during this period, renin was >500 pg/mL (2.13-58.78) and aldosterone was 32.08 ng/L (25-315). It was considered that the low renin value in the patient's

Table 1. Patient's laboratory results

Hormone	Result	Normal range
Serum cortisol (µg/dL)	40.2	4.3-22.4
ACTH (pg/mL)	9.07	0-46
17-OHP (ng/mL)	0.35	0.59-3.44
DHEAS (ug/dL)	<15	80-560
AS (ng/mL)	0.21	0.03-0.15
11-Deoxycortisol (ng/mL)	3.56	0.43-7.56
Aldosterone (ng/dL)	>20	0-19.9
Renin (ng/mL/hour)	<0.14	0.06-4.69

ACTH: adrenocorticotropic hormone, 17-OHP: 17-hydroxyprogesterone, DHEAS: dehydroepiandrosterone sulfate, AS: androstenedione

tests taken in the pediatric intensive care unit was due to the fludrocortisone treatment, and the high aldosterone value was thought to be due to analytical interference caused by the medication.

In the metabolic tests of the patient, serum CPK was found to be 40,800 U/L (normal range: 46-171), and the lipid panel showed elevated triglycerides at 637 mg/dL (normal range: 0-150). Urinary organic acid analysis using gas chromatography-mass spectrometry (GC-MS) revealed a high urinary glycerol excretion of 1465.14 mmol/mmol creatinine (normal range: 0.01-0.1) (Figure 1 and 2). The positive urinary glycerol level and triglyceridemia suggested GKD.

Abdominal ultrasound failed to visualize the adrenal glands. Scrotal ultrasound showed the right testis in the proximal inguinal canal (undescended testis) measuring 16x8x6 mm (0.4 mL), while the left testis was not visualized. Bilateral adrenal glands could not be seen on upper abdominal magnetic resonance imaging (MRI). The clinical and laboratory observations were obtained following an AHC diagnosis. The brain MRI showed widespread diffusion restrictions in both cerebral and cerebellar hemispheres, as well as in the basal ganglia.

Peripheral blood chromosome analysis reported a karyotype of 46,XY. An array CGH test was performed to investigate submicroscopic deletions. The microarray analysis result was arr[GRCh37] Xp21.3p21.1(28514128_37189187)x0. A hemizygous deletion of approximately 8.6 Mb was detected in the patient (Figure 3). The deletion encompassed the *IL1RAPL1*, *NR0B1* (*DAX1*), *GK*, and also the *DMD* genes. Thus he was diagnosed with Xp21 contiguous gene deletion syndrome, characterized by GKD, AHC, and possible DMD.

During the follow-up, the patient did not experience any vomiting, could tolerate feeding, and gained weight. Laboratory tests indicated that electrolyte values remained within normal ranges. On the 32nd day of hospitalization, he was discharged on oral hydrocortisone and fludrocortisone treatments. He was placed under multidisciplinary follow-up involving the relevant specialties.

Discussion

In this article, we present our experience in the diagnosis and treatment of a patient who was referred at 8 months and 13 days of age with complaints of respiratory distress, dehydration, and hypoglycemia. Cytogenetic and molecular studies confirmed a deletion involving the *GK*, *NR0B1*, and *DMD* genes. The patient is currently under multidisciplinary follow-up, and appropriate care is provided in a supervised institutional setting with regular medical oversight.

CGKD is an X-linked inherited contiguous gene deletion syndrome. It usually results from a partial deletion at the Xp21 chromosomal locus, encompassing genes linked to GKD, AHC, DMD, and several developmental disorders. The symptoms are

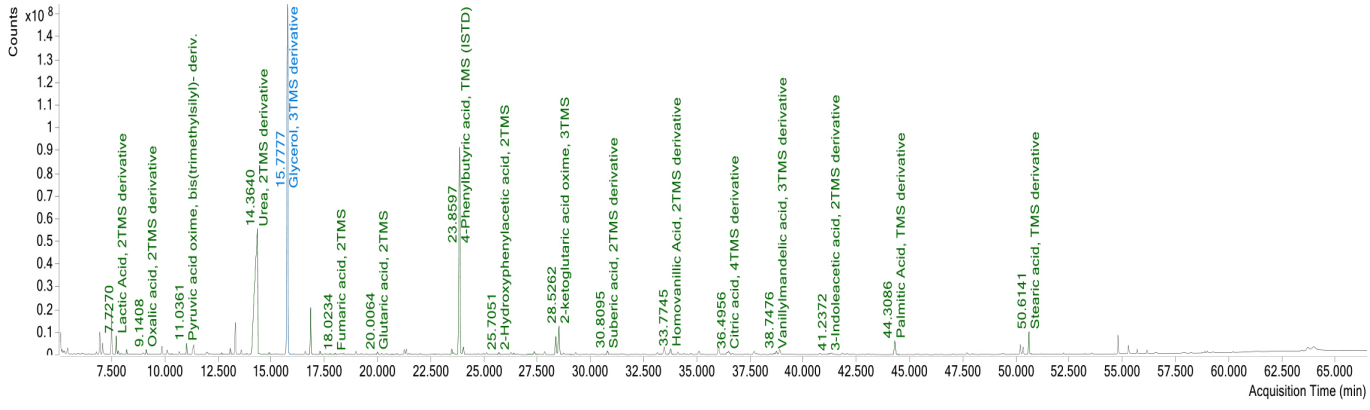

Figure 1. Urinary organic acid analysis results

associated with the extent of the deletion and can manifest in early life, as in the presented case (4). Due to its rarity and limited recognition among healthcare providers, CGKD is frequently challenging to diagnose in its early stages. Most affected individuals are male, and to date, there have been fewer than ten reported cases of female patients (5,6).

In the presented case, adrenal insufficiency was considered due to salt loss during the neonatal period, and treatment with hydrocortisone, fludrocortisone, oral salt, and anti-potassium medications was initiated. The clinical and laboratory findings of dehydration, hyponatremia, hyperkalemia, and hyperpigmentation were consistent with the diagnosis of adrenal insufficiency. It was suggested that the normal serum ACTH level might be due to early steroid replacement therapy. Congenital adrenal hyperplasia (CAH) is the most common cause of primary adrenal insufficiency; however, a 17-OHP level below 10 ng/mL during the neonatal period effectively excludes this diagnosis (7). In addition, CAH is typically associated with enlarged adrenal glands on imaging (8). In the presented case, the adrenal glands were not visualized even on MRI, supporting the diagnosis of AHC. The findings in our patient are consistent with AHC, which may be linked to mutations or deletions in the *DAX-1* (*NR0B1*) gene on the X chromosome (9,10), abnormalities in the steroidogenic factor 1 gene on chromosome 9q33 (11), and disorders like IMAGe syndrome (12). In X-linked AHC, deletions of the *DAX-1* gene can occur along with deletions of adjacent genes in the Xp21 locus.

In our case, the lipid metabolism findings prompted us to consider CGKD. The deletion of the GK locus causes GKD, which is linked to hypertriglyceridemia. Elevated triglyceride levels in lipid metabolism tests should raise concern for CGKD in an infant with growth delay. A fast and straightforward method for diagnosing CGKD is by measuring urinary glycerol levels using GC-MS analysis (13). Following this, genetic screening can verify the deletion of the CGKD loci.

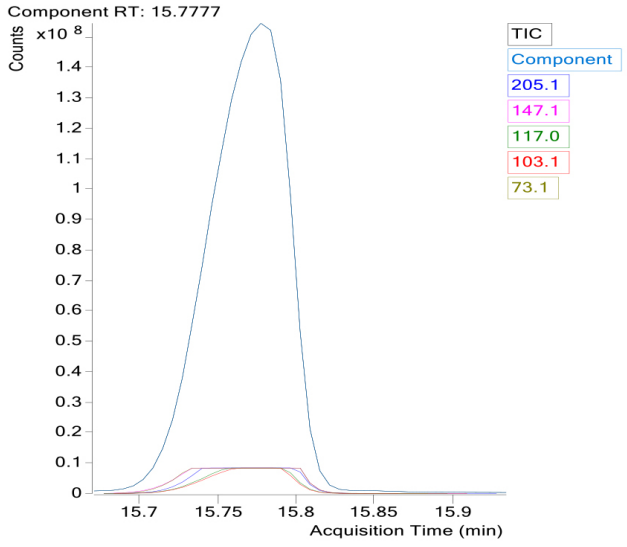

Figure 2. Glycerol peak in urinary organic acid analysis

Figure 3. 656K Microarray Analysis DECIPHER image of the region between p21.3 and p21.1 on the Grch37 X Chromosome (28514128-37189187). The layout of morbid genes *IL1RAPL1*, DMD, GK, *NR0B1, CFAP47* in the deleted area and the locations of all other genes in this region are shown

Glycerol kinase (IUB: 2.7.1.30) is the enzyme responsible for phosphorylation of glycerol from triglyceride breakdown for further metabolism. The absence of this enzyme activity leads to the accumulation of glycerol in circulation, causing glycerolaemia and glyceroluria (14,15). The glycerolaemia is usually detected as pseudo-hypertriglyceridemia due to overestimation of serum triglyceride levels as a result of analytical interference by free glycerol on the assay method (16).

Hypoglycemia is a feature in both congenital adrenal hypoplasia and GKD. In congenital adrenal hypoplasia, hypoglycemia is due to the deficiency of the counterregulatory hormone cortisol. In GKD, the conversion of glycerol to glycerol-3-phosphate is impaired, limiting substrate for gluconeogenesis. Thus, in Xp21 contiguous gene deletion, hypoglycemia results from a combination of congenital adrenal hypoplasia and GKD.

DMD symptoms in infants are frequently challenging to identify; nevertheless, caregivers should consult a doctor if their child cannot sit up by six months or older. In the presented case, psychometric analysis revealed that the patient was behind peers at all developmental stages. In clinical practice, the possibility of DMD can be considered based on laboratory results. Serum CPK levels are typically significantly elevated, usually 10 to 20 times higher than the normal reference range (17). In the presented case, the serum CPK concentration was noted to be significantly elevated. In addition, mental retardation may accompany DMD in male patients (18).

Table 2 lists 21 cases diagnosed with Contiguous Gene Deletion Syndrome and published since the 2000s. Genetic diagnosis was available for all cases except one (20). In two cases, other than *DMD*, the other genes were not investigated (3). Adrenal insufficiency was present in 14 cases (2,3,4,19,20,24,26,28,29,30). In 12 of these cases, a deletion in the *NR0B1* gene was present, while in the other two cases, the *NR0B1* gene was not investigated (3,23). Dysmorphic features have been inconsistently reported in the literature, and most reports do not describe these features in detail, making it difficult to define a consistent phenotypic pattern.

Table 2. Clinical and laboratory features of reported cases with contiguous gene deletion syndrome involving *DMD, GK, NR0B1*, and *IL1RAPL1* genes

Reference	Gender	Age of diagnosis	Genetic variants	Symptoms	Na meq/L	K meq/L	Serum cortisol	ACTH	CPK U/L	Urinary glycerol excretion
Our case	M	8 months	*DMD, NR0B1, GK, IL1RAPL1*	Respiratory distress, dehydration, hypoglycemia, dark skin	129	6.4	40.2 µg/dL (4.3-22.4) (At)	9.07 pg/mL (0-46) (At)	40.800	1465.14 mmol/mmol creatinine
Islas Abdenur (20) 2024	M	14 days	Not investigated	Dehydration, hyponatremia, hyperkalemia	126	5.9	5.9 ug/dL	480 pg/mL	6.530	Massive glyceroluria (Value not specified)
Pizza et al. (21) 2023	M	7 months	*DMD, GK*	Development delay, hypotonia, unable to walk, to go upstairs, to sit, intellectual disability	-	-	-	-	14.576	1082 mM/Mcreat
Bi et al. (22) 2023	M	19 days	*DMD, GK, CFAP47, CYBB, XK, RPGR*	Macrosomia, neonatal sepsis, liver and lung abscesses	-	-	-	-	1.115	-
Tao (19) et al. 2022	M	48 days	*DMD, GK, NR0B1*	Growth retardation, vomiting, dark skin, failure to thrive	132	5.9	647.9 nmol/L (66-630)	15.04 pg/mL (7.2-63.6)	1.586	3129.2 umol/mmol
Rathnasiri et al. (23) 2021	M	36 months	*DMD* (exons 45-79), *GK*	Failure to thrive, difficulty in feeding, developmental delay, difficulty in walking and getting up from the seated position, Gower's sign, calf hypertrophy	120	7.1	4 nmol/L (120-626)	343 pg/mL (7-41)	12.395	Massive glyceroluria (Value not specified)

Table 2. Clinical and laboratory features of reported cases with contiguous gene deletion syndrome involving *DMD, GK, NR0B1*, and *IL1RAPL1* genes

Reference	Gender	Age of diagnosis	Genetic variants	Symptoms	Na meq/L	K meq/L	Serum cortisol	ACTH	CPK U/L	Urinary glycerol excretion
Wikiera et al. (24) 2021 *Patient 1*	M	5 weeks	*NR0B1, GK, DMD*	Failure to thrive, loss of body weight, athrepsia, dehydration, weak muscle tone, psychomotor development delay	116.6	6.1	46.92 nmol/l	162 ng/L (<45)	13.126	Massive glyceroluria (Value not specified)
Wikiera et al. (24) 2021 *Patient 2*	M	5 weeks	*NR0B1, GK, IL1RAPL1, DMD* (*C*-terminal region)	Dehydration, adynamia, failure to thrive, psychomotor development delay	123	6.1	-	-	4.236	-
Liu et al. (25) 2021	M	Data not available	*IL1RAPL1, MAGEB1-4, ROB, CXorf2, M, AP3K71P, FTHL1, DMD, FAM47A, TMEM47, FAM47B*	Data not available						
Korkut et al. (4) 2016 *Patient 1*	M	36 days	*DMD* (part), *GK, NR0B1, IL1RAPL1* (part)	Difficulty to feed, vomiting, weight loss, dark skin, hypotonia, dehydration, dysmorphic facial features	128	8.6	12.6 µg/dL	>2000 pg/mL	5.758	4847.6 mmol/mmol creatine
Korkut et al. (4) 2016 *Patient 2*	M	18 days	DMD, GK, NR0B1	Reduced breastfeeding, vomiting, weight loss, dehydration, dysmorphic facial features	124	7.4	20.6 µg/dL	628 pg/mL	28.134	-
Heide et al. (5) 2015 *Patient 1*	F	-	*IL1RAPL1, NR0B1, GK, DMD* (last 37 exons)	Delayed expressive language, hyperopia, multiple serous otitis, intellectual disability	-	-	-	-	Normal (Value not specified)	-
Heide et al. (5) 2015 *Patient 2*	F	-	*IL1RAPL1, NR0B1, GK, DMD* (last 22 exons)	Delayed expressive language, muscular pains, muscular fatigue, global muscular hypertrophy, epilepsy	-	-	-	-	579	-
Sevim et al. (26) 2011	M	1 month	*DMD* (exons 62-79), *GK, NR0B1, IL1RAPL1*	Hypotonia, inadequate breastfeeding, failure to thrive, decreased skin turgor, scrotal hyperpigmentation	124	6.9	184.9 nmol/L (185-624)	4.58 pmol/L (0-50)	7.019	Massive glyceroluria (Value not specified)

Table 2. Clinical and laboratory features of reported cases with contiguous gene deletion syndrome involving *DMD, GK, NR0B1*, and *IL1RAPL1* genes

Reference	Gender	Age of diagnosis	Genetic variants	Symptoms	Na meq/L	K meq/L	Serum cortisol	ACTH	CPK U/L	Urinary glycerol excretion
Ramanjam et al. (3) 2010 *Patient 1*	M	19 days	*DMD*; other genes were not investigated	Dehydration, poor feeding, vomiting, developmental delay, hypotonia global weakness, calf hypertrophy; reflexes absent, intellectual disability	117	8.5	478 nmol/L (28-662)	-	2.507	590 mmol/L
Ramanjam et al. (3) 2010 *Patient 2*	M	Prenatal	*DMD*; other genes were not investigated	Hypotonia, waddling gait, difficulty in climbing stairs, intellectual disability	-	-	-	-	5.307	220 mmol/L
Jamroz et al. (27) 2010	M	4 months	*DMD, GK*	Failure to thrive, dehydration global developmental delay, axial hypotonia, distal hypertonia, intellectual disability	-	-	-	-	10.818	Massive glyceroluria (Value not specified)
Sanz-Ruiz et al. (28) 2009	M	7 months	*DMD, GK, NR0B1, IL1RAPL1*	Global developmental delay, pronounced axial hypotonia, intellectual disability	-	-	9.8 µg/dL (4-19.4)	>1.250 pg/mL (0-46)	12.829	12.332 µM/mol creatinin
Pantoja-Martínez et al. (29) 2007	M	8 days	*DMD, GK, NR0B1*	Salt loss with lethargy, vomiting, hypoglycemia, metabolic acidosis, progressive muscle weakness, intellectual disability	121	7.5	1 µg/dL (12-960)	807 pg/mL (16-106)	9.700	6.173 µmol/mol creatinin
Sehgal and Stack (2) 2005	M	Newborn	*GK, NR0B1*	Hypoglycemia, salt loss	126	5.9	69 mmol/L (85-440)	32 pmol/L (<10)	Normal (Value not specified)	Massive glyceroluria (Value not specified)
Ma et al. (30) 2004	M	42 months	*DMD* (exons 62-66), *GK, NR0B1*	Nausea, vomiting, global development delay, unable to walk, go upstairs, run fast, Gower's Sign, calf hypertrophy, intellectual disability	126	6.6.	3.5 ng/dL (5-25)	-	5.798	-

DMD: Duchenne muscular dystrophy, *GK*: glycerol kinase, *NR0B1*: nuclear receptor superfamily 0, group B, member 1, *IL1RAPL1*: interleukin 1 receptor accessory protein-like 1, M: male, F: female, At: after treatment

More than 100 male patients have been reported so far, while only a few cases of symptomatic female carriers have been described. In two of the reported cases, detailed clinical features and X chromosome inactivation analysis are presented in two unrelated female patients with overlapping Xp21 deletions, who presented with intellectual disability and episodic muscular symptoms (5).

As in our case, elevated CPK levels were detected in cases with *DMD* gene deletions. Only in one of the two female cases, CPK levels were found to be normal (5).

In 11 of the 17 cases with a deletion in the *GK* gene, glyceroluria was reported, as in our case (2,16,19,21,23,24,26,27,28,29). In six cases, no results were provided. In one case, despite massive glyceroluria, genetic testing was not performed (20).

Generally, corticosteroid therapy and salt intake are accepted treatments for CGKD (2,4). Diagnosing CGKD can be difficult, but a detailed standard assessment can help identify pseudo-hypertriglyceridemia and elevated CPK levels, which can then lead to additional genetic testing. The dosage of corticosteroid substitution treatment should be dynamically adjusted to avoid negatively impacting the hypothalamic-pituitary-adrenal axis and to minimize unwanted effects on the child's immune system (19). Furthermore, this treatment should be carefully managed and dynamically adjusted to minimize the risk of adrenal crisis.

Conclusion

This case presentation highlights the medical and genetic diversity of the very rare Xp21 contiguous gene deletion syndrome. The dysmorphic features described in our patient, including upward-deviated eyes and low-set ears, in combination with adrenal insufficiency and features of GKD, supported the diagnosis and emphasized the importance of a multidisciplinary approach. The response to treatment was positive, leading to stabilization. This case highlights the importance of clinical practice in diagnosing and managing rare genetic syndromes. AHC and CGKD should be included in the differential diagnosis of male newborns exhibiting similar clinical symptoms and adrenal imaging may provide key diagnostic data. Performing genetic analyses aids in confirming the diagnosis by pinpointing the position and size of deletions, predicting prognosis, and identifying female carriers.

Ethics

Informed Consent: Written informed consent of the parents was obtained for this case report.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Berna Singin, Zeynep Donbaloğlu, Ebru Barsal Çetiner, Aynur Bedel, Kürşat Çetin, Belgin Akcan Paksoy, Hale Ünver Tuhan, Mesut Parlak, Concept: Berna Singin, Hale Ünver Tuhan, Mesut Parlak, Design: Berna Singin, Zeynep Donbaloğlu, Mesut Parlak, Data Collection or Processing: Berna Singin, Zeynep Donbaloğlu, Ebru Barsal Çetiner, Aynur Bedel, Kürşat Çetin, Mesut Parlak, Analysis or Interpretation: Berna Singin, Tarkan Kalkan, Halide Akbaş, Mesut Parlak, Literature Search: Berna Singin, Hale Ünver Tuhan, Mesut Parlak, Writing: Berna Singin, Mesut Parlak.

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