Case Report

DOI: 10.4274/jcrpe.galenos.2026.2025-11-8

Primary Adrenal Insufficiency in Pseudo-Neonatal Adrenoleukodystrophy Case Report

İhsan Turan[1], Fatma Derya Bulut[2], Leman Damla Kotan[1], Ayşe Merve Çimen[1], Deniz Kor[2], Eda Mengen[1], Neslihan Önenli Mungan[2]
[1]Çukurova University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Endocrinology, Adana, Türkiye
[2]Çukurova University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Metabolism and Nutrition, Adana, Türkiye

What is already known on this topic?
• Biallelic pathogenic variants in *ACOX1* cause the peroxisomal disorder pseudo-neonatal adrenoleukodystrophy
• Literature reports—albeit from very few publications—ACOX1-associated pseudo-neonatal adrenoleukodystrophy with adrenal pathology; however, its contribution to adrenal insufficiency is not widely recognized.

What this study adds?
• In conditions that cause adrenal insufficiency, such as peroxisomal disorders, the overall clinical course may obscure the manifestations of adrenal insufficiency, resulting in delayed recognition or missed diagnosis.

Abstract
Primary adrenal insufficiency (PAI) in childhood is a rare and potentially life-threatening condition that may arise from defects in adrenal steroidogenesis, adrenal dysgenesis, ACTH resistance, autoimmune mechanisms, or inherited metabolic disorders. Among the latter, peroxisomal dysfunctions represent a rare cause. Although X-linked adrenoleukodystrophy is a well-recognized etiology, adrenal involvement in other peroxisomal diseases, such as ACOX1 deficiency, remains poorly defined. We report a three-year-old girl with global developmental delay, epilepsy, bilateral sensorineural hearing loss, and progressive neurological regression. Biochemical analyses revealed abnormal plasma very-long-chain fatty acids profile, suggesting a peroxisomal disorder. Whole-exome sequencing identified a homozygous pathogenic variant (c.1478+2T>A) in *ACOX1*, confirming the diagnosis of pseudo-neonatal adrenoleukodystrophy. During hospitalization for a urinary tract infection, endocrine evaluation revealed markedly elevated plasma ACTH (529 pg/mL) and low serum cortisol (8.62 µg/dL), while Na, K, and PRA were within normal limits. Adrenal imaging was consistent with atrophy. Hydrocortisone replacement was initiated with good clinical response. Notably, the patient had no classical signs of adrenal failure such as hyperpigmentation or electrolyte imbalance. This case provides additional evidence that ACOX1-related Pseudo-neonatal adrenoleukodystrophy may be associated with variable adrenal involvement, expanding the phenotypic spectrum of the disorder. The absence of typical clinical manifestations highlights the importance of routine hormonal screening in children with peroxisomal diseases, even in the absence of overt adrenal symptoms. Early recognition of endocrine dysfunction can prevent life-threatening adrenal crises and offers valuable insight into the broader pathophysiology of peroxisomal β-oxidation disorders.
Keywords: ACOX1, primary adrenal insufficiency, pseudo-neonatal adrenoleukodystrophy

Asst. Prof. Dr. İhsan Turan, Çukurova University Faculty of Medicine, Department of Pediatrics, Division of Pediatric Endocrinology, Adana, Türkiye
ituran@cu.edu.tr
0000-0002-5654-247X

14.11.2025
03.03.2026

Epub: 09.03.2026

Introduction
Primary adrenal insufficiency (PAI) in children is a rare disorder that may arise from hereditary causes or, less commonly, from acquired conditions. It is characterized by deficient production of glucocorticoids, with or without concomitant mineralocorticoid deficiency. When presenting in early life, PAI is almost exclusively of genetic origin. The predominant cause of PAI in children is congenital adrenal hyperplasia (CAH) resulting from 21-hydroxylase deficiency, which accounts for nearly 95% of cases. Beyond defects in steroidogenesis—primarily CAH—the genetic etiologies of PAI can be categorized into adrenal dysgenesis, ACTH resistance syndromes, autoimmune conditions, and various inherited metabolic disorders (1,2). Metabolic causes of PAI include: (a) peroxisomal disorders, such as Zellweger spectrum disorders and X-linked or neonatal adrenoleukodystrophy; (b) mitochondrial defects, including MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) and Kearns–Sayre syndrome; and (c) abnormalities in cholesterol biosynthesis, most notably Smith–Lemli–Opitz syndrome (3). The exact proportion of PAI cases attributable to mutations in currently recognized genes is not well established, and it is plausible that some patients may still harbor etiologies of yet unidentified genetic origin (4). In this article, we present a case of adrenal insufficiency associated with a likely pathogenic variant in the *ACOX1* gene, whose relationship with adrenal insufficiency has not been widely recognized.

Case Report
A three-year-old girl was admitted for etiological evaluation due to bilateral sensorineural hearing loss (SNHL), refractive error, developmental delay, neurological regression, and epilepsy. She was born at term following an uncomplicated pregnancy and delivery, with a birth weight of 2950 grams. Following birth, the patient required hospitalization. Seizure activity was first observed within the first week of life, and antiepileptic therapy was initiated at two months of age. She has since maintained levetiracetam monotherapy. Bilateral sensorineural hearing loss (SNHL) was identified at 1.5 years of age, despite normal otoacoustic emissions and auditory brainstem response (ABR) results during the neonatal period. Corrective eyeglasses had been prescribed one year earlier for refractive error (hyperopia, –11 D). According to her parents, her visual performance was notably poorer under dim illumination. She exhibited global developmental delays, achieving head control at 6 months and the ability to sit with support at 11 months. Although she never attained independent ambulation, she was able to stand with assistance at 2 years of age. Over the preceding nine months, she experienced a progressive loss of motor abilities and was bedridden at the time of admission. The parents were consanguineous, being first-degree cousins. The patient had two healthy sisters. Her weight standard deviation score (SDS) was –1.98 and height SDS was –2.3. Physical examination revealed frontal bossing, large ears, axial hypotonia, spasticity of the extremities, and hypoactive deep tendon reflexes. She was using both a hearing aid and corrective

eyeglasses. Given the clinical suspicion of a peroxisomal disorder, plasma very-long-chain fatty acid (VLCFA) analysis demonstrated an abnormal profile (elevated plasma concentrations of C26:0, along with increased C24/C22 and C26/C22 ratios), while phytanic and pristanic acid levels remained within normal limits. Whole-exome sequencing identified a homozygous c.1478+2T>A variant in the *ACOX1* gene. Whole-exome sequencing was performed by the MGI-DNBSEQ-G400 instrument. Validation of the WES findings and segregation analysis were performed using the Illumina MiSeq platform (Figure 1) (5). The identified variant was classified as pathogenic (PVS1, PM2) according to the American College of Medical Genetics and Genomics (ACMG) criteria. No further pathogenic variants were detected in any gene implicated in the etiology of adrenal insufficiency (3). Both parents were heterozygous carriers of the same variant, and the segregation pattern supported autosomal recessive inheritance. SpliceAI strongly supported a splice-altering impact, with a prediction score of 0.99 (range, 0-1) (6). The patient was admitted to the hospital with fatigue secondary to a urinary tract infection. Without any signs and symptoms of adrenal insufficiency (hyperpigmentation, electrolyte imbalance, hypoglycemia, or metabolic acidosis, etc.), however, adrenocorticotropic hormone (ACTH) and cortisol tests were requested for further assessment. The plasma ACTH concentration was 529 pg/mL, and the serum cortisol level measured 8.62 µg/dL which were compatible adrenal insufficiency. Plasma glucose level: 95 ng/dL, arterial blood pressure 90/60 mmHg, DHEA-S: 1.4 ug/dL. The plasma renin activity (PRA) and blood aldosterone levels were not consistent with an indication for fludrocortisone (Na: 138 mEq/L K: 4.22 mEq/L PRA: 211 ng/dL/Hr (50-585), Aldosterone 13.7 pg/mL (3-35). Oral hydrocortisone therapy was initiated at a dose of 8 mg/m²/day. Computed tomography (CT) imaging revealed bilateral adrenal atrophy (Figure 2). Later, during empiric antibiotic therapy for suspected urinary tract infection, the ACTH level was 1085 pg/mL and the serum cortisol was 0.29 µg/dL. Stress-dose hydrocortisone was administered as part of cortisol replacement, and the treatment proceeded without adrenal complications.

Discussion

The case of adrenal insufficiency diagnosed as pseudo-neonatal adrenoleukodystrophy, notable for the absence of mineralocorticoid requirement, represents a distinctive contribution to the literature, as underscoring the clinical heterogeneity and expanding the molecular spectrum.

Peroxisomal disorders represent a subset of inherited metabolic causes of primary adrenal insufficiency (PAI). Among these, X-linked adrenoleukodystrophy (OMIM: 300100)—attributable to pathogenic variants in ABCD1—is the most widely recognized. Moreover, the associations of neonatal adrenoleukodystrophy (OMIM: 601539), infantile Refsum disease (OMIM:266500), and Zellweger syndrome (OMIM: 214100) with adrenal insufficiency have been delineated in the literature. Peroxisomal acyl-CoA oxidase 1 (ACOX1) catalyzes the FAD-dependent oxidation of acyl-CoAs to 2-trans-enoyl-CoAs, the first and rate-limiting step of peroxisomal fatty-acid β-oxidation. Pseudo-neonatal adrenoleukodystrophy (Pseudo-NALD), resulting from biallelic pathogenic variants in *ACOX1*, is so named for its clinical and biochemical resemblance to neonatal adrenoleukodystrophy, an established cause of adrenal insufficiency (4,7). Pseudo-NALD, with a prevalence of <1:1,000,000, is characterized by a heterogeneous spectrum of genetic variants and is marked by the elevated plasma concentrations of C26:0, along with increased C24/C22 and C26/C22 ratios in plasma. Clinically, it manifests with hypotonia, seizures, and early-onset leukodystrophy, typically culminating in death during early childhood (8).

A review of the literature reported cases of Pseudo-NALD associated with *ACOX1* pathogenic variants, in which adrenal gland pathology was noted. However, the disorder is not yet clearly recognized as a definitive cause of adrenal insufficiency (9,10,11,12). Similarly, in recent reviews addressing the etiology of adrenal insufficiency, Pseudo-NALD is not listed among the recognized or potential causes (13). Most recently, Helvacıoglu and colleagues published a pivotal study that directly addressed this question, providing compelling evidence that biallelic *ACOX1* pathogenic variants may indeed contribute to the development of adrenal insufficiency, thereby strengthening the causal association between ACOX1 dysfunction and adrenal pathology (4). In the referenced study, the patient—aged 1.5 years—demonstrated adrenal gland atrophy on imaging. Similarly, adrenal imaging in the present case revealed structurally normal adrenal glands. Our case, characterized by a milder clinical presentation of adrenal insufficiency and diagnosed incidentally, contrasts with the recently reported case, which exhibited a more severe clinical course and required mineralocorticoid replacement therapy. This case provided a clinically valuable insight, as the diagnosis was established by investigating the association between peroxisomal disease and adrenal insufficiency in the absence of classical clinical manifestations such as hyperpigmentation, hyponatremia, hyperkalemia, or hypoglycemia. Upon detailed analysis, we observed that the two previously reported cases exhibiting more pronounced features of adrenal insufficiency were both diagnosed at an earlier age. In these cases, adrenal insufficiency was diagnosed in infancy with significant salt wasting. In contrast, our case was diagnosed based on cortisol levels without any hyponatremia, hyperkalemia, or dehydration. Hence, our case appears to show a milder phenotype of adrenal insufficiency compared to these cases (4,9). In four cases, including the present one, clinical manifestations of adrenal insufficiency were relatively mild and were not accompanied by life-threatening features such as significant salt and water loss (10,11,12). This observation suggests that Pseudo-NALD may encompass two distinct phenotypic subtypes associated with adrenal insufficiency—one characterized by mild, and the other by severe, adrenal insufficiency. However, independent of phenotypic severity, it should be emphasized that in disorders associated with adrenal insufficiency, such as peroxisomal diseases, the broader clinical course may mask the manifestations of adrenal insufficiency, leading to delayed recognition or missed diagnosis. Given that Pseudo-NALD is a potentially fatal disorder of childhood, it is plausible that unrecognized abnormalities in ACTH and cortisol levels may exist in cases without comprehensive hormonal evaluation. In light of our experience with this case, we propose that disorders resembling those currently recognized among the causes of adrenal insufficiency may represent potential novel candidates within its etiologic spectrum. The identification of two cases of such a rare disorder from the same country within a relatively short time interval is noteworthy. However, we do not possess data supporting an ethnicity-specific predisposition. Rather, we attribute this observation to the relatively higher frequency of rare autosomal recessive diseases, likely related to the persistent high rate of consanguineous marriages in Türkiye. This case harbored a novel splice donor variant. It met pathogenicity criteria owing to its null effect (PVS1) and lack of representation in gnomAD (PM2). In conjunction with the observed phenotypic features, the variant was considered disease-causing despite the absence of functional assays.

In conclusion, we believe that the present case expands the recognized spectrum of adrenal involvement in pseudo-neonatal adrenoleukodystrophy, a rare and complex disorder, and provides valuable insights that may guide future research into its pathophysiology and clinical variability.

Statements

Statement of Ethics

Written informed consent was obtained from the participants' parent/legal guardian for publication of the details of their medical case.

Conflict of Interest Statement

All authors report no competing interests.

We used ChatGPT (OpenAI) for English language editing.

References

1. Camtosun E, Dundar I, Akinci A, Kayas L, Ciftci N. Pediatric Primary Adrenal Insufficiency: A 21-year Single Center Experience. J Clin Res Pediatr Endocrinol 2021;13:88-99. Epub 20200917

2. Capalbo D, Moracas C, Cappa M, Balsamo A, Maghnie M, Wasniewska MG, Greggio NA, Baronio F, Bizzarri C, Ferro G, Di Lascio A, Stancampiano MR, Azzolini S, Patti G, Longhi S, Valenzise M, Radetti G, Betterle C, Russo G, Salerno M. Primary Adrenal Insufficiency in Childhood: Data From a Large Nationwide Cohort. J Clin Endocrinol Metab 2021;106:762-773.

3. Malikova J, Fluck CE. Novel insight into etiology, diagnosis and management of primary adrenal insufficiency. Horm Res Paediatr 2014;82:145-157. Epub 20140801
4. Helvacioglu D, Canbaz AT, Tekmenuray-Unal A, Ada Y, Yapici O, Genc E, Kilavuz S, Gurpinar Tosun B, Ozturk Hismi B, Guran T. Primary adrenal insufficiency caused by pseudo-neonatal adrenoleukodystrophy associated with biallelic ACOX1 mutations. Eur J Endocrinol 2025;192:K38-K43.
5. Bentley DR, Balasubramanian S, Swerdlow HP, Smith GP, Milton J, Brown CG, Hall KP, Evers DJ, Barnes CL, Bignell HR, Boutell JM, Bryant J, Carter RJ, Keira Cheetham R, Cox AJ, Ellis DJ, Flatbush MR, Gormley NA, Humphray SJ, Irving LJ, Karbelashvili MS, Kirk SM, Li H, Liu X, Maisinger KS, Murray LJ, Obradovic B, Ost T, Parkinson ML, Pratt MR, Rasolonjatovo IM, Reed MT, Rigatti R, Rodighiero C, Ross MT, Sabot A, Sankar SV, Scally A, Schroth GP, Smith ME, Smith VP, Spiridou A, Torrance PE, Tzonev SS, Vermaas EH, Walter K, Wu X, Zhang L, Alam MD, Anastasi C, Aniebo IC, Bailey DM, Bancarz IR, Banerjee S, Barbour SG, Baybayan PA, Benoit VA, Benson KF, Bevis C, Black PJ, Boodhun A, Brennan JS, Bridgham JA, Brown RC, Brown AA, Buermann DH, Bundu AA, Burrows JC, Carter NP, Castillo N, Chiara ECM, Chang S, Neil Cooley R, Crake NR, Dada OO, Diakoumakos KD, Dominguez-Fernandez B, Earnshaw DJ, Egbujor UC, Elmore DW, Etchin SS, Ewan MR, Fedurco M, Fraser LJ, Fuentes Fajardo KV, Scott Furey W, George D, Gietzen KJ, Goddard CP, Golda GS, Granieri PA, Green DE, Gustafson DL, Hansen NF, Harnish K, Haudenschild CD, Heyer NI, Hims MM, Ho JT, Horgan AM, Hoschler K, Hurwitz S, Ivanov DV, Johnson MQ, James T, Huw Jones TA, Kang GD, Kerelska TH, Kersey AD, Khrebtukova I, Kindwall AP, Kingsbury Z, Kokko-Gonzales PI, Kumar A, Laurent MA, Lawley CT, Lee SE, Lee X, Liao AK, Loch JA, Lok M, Luo S, Mammen RM, Martin JW, McCauley PG, McNitt P, Mehta P, Moon KW, Mullens JW, Newington T, Ning Z, Ling Ng B, Novo SM, O'Neill MJ, Osborne MA, Osnowski A, Ostadan O, Paraschos LL, Pickering L, Pike AC, Pike AC, Chris Pinkard D, Pliskin DP, Podhasky J, Quijano VJ, Raczy C, Rae VH, Rawlings SR, Chiva Rodriguez A, Roe PM, Rogers J, Rogert Bacigalupo MC, Romanov N, Romieu A, Roth RK, Rourke NJ, Ruediger ST, Rusman E, Sanches-Kuiper RM, Schenker MR, Seoane JM, Shaw RJ, Shiver MK, Short SW, Sizto NL, Sluis JP, Smith MA, Ernest Sohna Sohna J, Spence EJ, Stevens K, Sutton N, Szajkowski L, Tregidgo CL, Turcatti G, Vandevondele S, Verhovsky Y, Virk SM, Wakelin S, Walcott GC, Wang J, Worsley GJ, Yan J, Yau L, Zuerlein M, Rogers J, Mullikin JC, Hurles ME, McCooke NJ, West JS, Oaks FL, Lundberg PL, Klenerman D, Durbin R, Smith AJ. Accurate whole human genome sequencing using reversible terminator chemistry. Nature 2008;456:53-59.
6. Jaganathan K, Kyriazopoulou Panagiotopoulou S, McRae JF, Darbandi SF, Knowles D, Li YI, Kosmicki JA, Arbelaez J, Cui W, Schwartz GB, Chow ED, Kanterakis E, Gao H, Kia A, Batzoglou S, Sanders SJ, Farh KK. Predicting Splicing from Primary Sequence with Deep Learning. Cell 2019;176:535-548 e524. Epub 20190117
7. Mohan S, Mayers M, Weaver M, Baudet H, De Biase I, Goldstein J, Mao R, McGlaughon J, Moser A, Pujol A, Suchy S, Yuzyuk T, Braverman NE. Evaluating the strength of evidence for genes implicated in peroxisomal disorders using the ClinGen clinical validity framework and providing updates to the peroxisomal disease nomenclature. Mol Genet Metab 2023;139:107604. Epub 20230511
8. Ferdinandusse S, Denis S, Hogenhout EM, Koster J, van Roermund CW, L IJ, Moser AB, Wanders RJ, Waterham HR. Clinical, biochemical, and mutational spectrum of peroxisomal acyl-coenzyme A oxidase deficiency. Hum Mutat 2007;28:904-912.
9. Suzuki Y, Shimozawa N, Yajima S, Tomatsu S, Kondo N, Nakada Y, Akaboshi S, Lai M, Tanabe Y, Hashimoto T, et al. Novel subtype of peroxisomal acyl-CoA oxidase deficiency and bifunctional enzyme deficiency with detectable enzyme protein: identification by means of complementation analysis. Am J Hum Genet 1994;54:36-43.
10. Poll-The BT, Roels F, Ogier H, Scotto J, Vamecq J, Schutgens RB, Wanders RJ, van Roermund CW, van Wijland MJ, Schram AW, et al. A new peroxisomal disorder with enlarged peroxisomes and a specific deficiency of acyl-CoA oxidase (pseudo-neonatal adrenoleukodystrophy). Am J Hum Genet 1988;42:422-434.
11. Carrozzo R, Bellini C, Lucioli S, Deodato F, Cassandrini D, Cassanello M, Caruso U, Rizzo C, Rizza T, Napolitano ML, Wanders RJ, Jakobs C, Bruno C, Santorelli FM, Dionisi-Vici C, Bonioli E. Peroxisomal acyl-CoA-oxidase deficiency: two new cases. Am J Med Genet A 2008;146A:1676-1681.
12. Naidu S, Hoefler G, Watkins PA, Chen WW, Moser AB, Hoefler S, Rance NE, Powers JM, Beard M, Green WR, et al. Neonatal seizures and retardation in a girl with biochemical features of X-linked adrenoleukodystrophy: a possible new peroxisomal disease entity. Neurology 1988;38:1100-1107.
13. Wijaya M, Huamei M, Jun Z, Du M, Li Y, Chen Q, Chen H, Song G. Etiology of primary adrenal insufficiency in children: a 29-year single-center experience. J Pediatr Endocrinol Metab 2019;32:615-622.

Figure 1: Next-generation sequencing (NGS) findings in the patient and parental segregation analysis
The top panel demonstrates that the proband is homozygous and red for the *ACOX1* variant (c.1478+2T>A), whereas the middle and bottom panels show that father and mother respectively is heterozygous for the same variant. The green box indicates the wild-type T nucleotide, whereas the red box highlights the mutant A nucleotide m: mutant, wt: wildtype

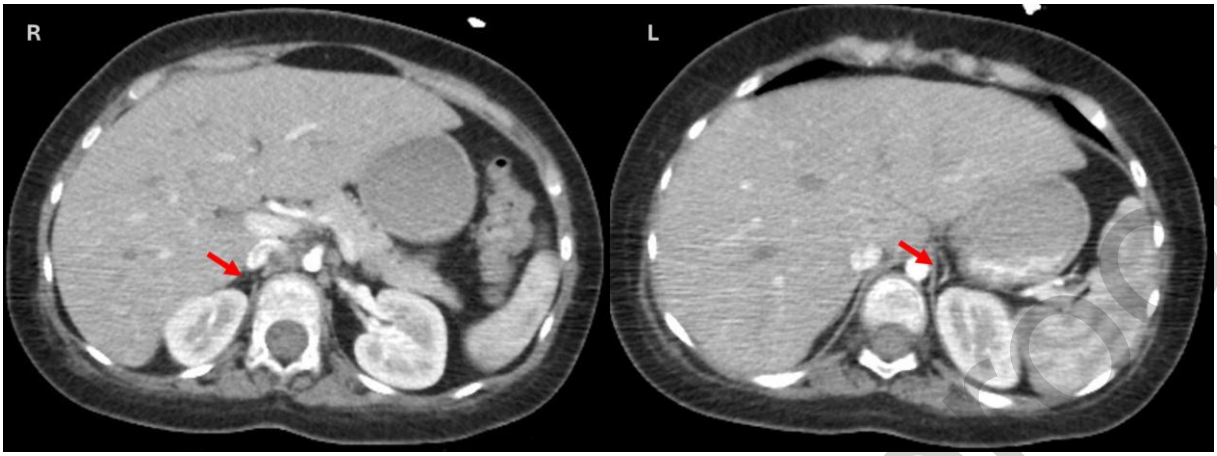

Figure 2: CT imaging of the patient's adrenal gland
Contrast-enhanced computed tomography images of the patient's right and left adrenal glands (arrows). R, right adrenal gland; L, left adrenal gland. The left adrenal gland demonstrates a genu measuring 2 mm, a medial limb of 1.3 mm, and a lateral limb of 1.0 mm, findings consistent with adrenal atrophy.