Cerebral, ocular, dental, auricular, skeletal anomalies (CODAS) syndrome: A case report

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Abstract. Cerebral, ocular, dental, auricular, skeletal anomalies (CODAS) syndrome is a rare multi-system developmental disorder. To date, only a few cases have been documented worldwide. The present case report describes the first case of CODAS syndrome in Iraq. A 4-year-old female patient of consanguineous parents who was diagnosed with CODAS syndrome, presented for a follow-up of bilateral ureterocutaneostomy due to renal disease. Her history of abnormalities began at birth when she was diagnosed with respiratory distress syndrome. At 2 months of age, she was diagnosed with adrenal neuroblastoma. At 5 months of age, she developed bilateral cataracts and then pseudoptosis. Subsequently, she underwent anoplasty to correct anal stenosis, which had been diagnosed at 45 days of age. At 23 months of age, magnetic resonance imaging of the spine demonstrated the loss of normal cervical lordosis. At 26 months of age, imaging of the lower limbs revealed bilateral coxa vara with irregular distal femoral development, absent femoral epiphyses, bilaterally absent patellae and knock knees. At 3 years of age, molecular genetic analysis confirmed CODAS syndrome with a homozygous Lon peptidase 1 (LONP1) gene variant (NM_004793.4 c.2008G>T; p. Ala670Ser). The syndrome poses challenges for clinicians, as it is extremely rare. The majority of documented cases of CODAS syndrome have been reported from Europe, the Americas, Saudi Arabia, Japan, Korea and China. To the best of our knowledge, no cases of CODAS syndrome have been documented within the Iraqi population to date. The first Iraqi case of CODAS syndrome, associated with a homozygous variant in the LONP1 gene (p. Ala670Ser), has been reported.

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Introduction

Cerebral, ocular, dental, auricular, skeletal anomalies (CODAS) syndrome, first identified by Shebib *et al* (1) in 1991, is a rare multi-system developmental disorder marked by cerebral, ocular, dental, auricular and skeletal anomalies. Given its rarity, to date, only a few cases have been documented worldwide (1-4). Its incidence is <1 in 1,000,000 children globally and typically manifests in the neonatal or infancy stage (3). Phenotypes of CODAS syndrome encompass a range of clinical manifestations, including growth retardation, intellectual disability, hypotonia with motor delays, epilepsy and craniofacial abnormalities. Additional features include delayed tooth eruption, enamel dysplasia, dens hypoplasia, cataracts, ptosis, scapha and helix dysplasia, and either conductive or sensorineural hearing loss. Short stature, skeletal dysplasia, scoliosis, genu valgus, pes valgus and vertebral coronal clefts have also been observed (5,6). The clinical presentation of CODAS syndrome may extend beyond the typical characteristics detailed in existing reports and could broaden as more

cases are documented (5,6). Although no curative treatment currently exists, rehabilitation may provide promising support for managing some drawbacks of this genetic condition (3,4). The majority of documented cases of CODAS syndrome have been reported from Europe, the Americas, Saudi Arabia, Japan, Korea and China (1-5,7-10). To the best of our knowledge, no cases of CODAS syndrome have been documented within the Iraqi population to date. The present study reports the case of a 4-year-old Iraqi female with CODAS syndrome.

Case report

The patient described herein was a 4-year-old female who had previously been diagnosed with CODAS syndrome (Fig. 1). She presented to Smart Health Tower (Sulaymaniyah, Kurdistan Region, Iraq) for a follow-up of bilateral ureterocutaneostomy, which had been performed at another center. She was born at 34 weeks of gestation to two Kurdish second-degree cousins via cesarean section due to intrauterine growth restriction. The mother was gravida 3, para 2, with one prior abortion. The patient's history of abnormalities began at birth when she was diagnosed with respiratory distress syndrome and required a 10-day admission to the intensive care unit. At 2 months of age, a contrast-enhanced computed tomography scan of the abdomen revealed a heterogeneous, hypodense mass measuring 38x36x35 mm in the left adrenal gland, situated above the left kidney, with mild compression of the upper pole. Under general anesthesia, the mass was excised through a left subcostal incision. A histopathological examination was performed on 5-μm-thick paraffin-embedded sections. The sections were fixed in 10% neutral buffered formalin at room temperature for 24 h and then stained with hematoxylin and eosin (H&E), Bio Optica Co. for 1-2 min at room temperature. The sections were then examined under a light microscope (Leica Microsystems GmbH). The histopathological analysis identified a 4x3.5x3.5 cm mass with histological features consistent with undifferentiated neuroblastoma, classified as stage 1 according to the International Neuroblastoma Pathology Classification and the International Neuroblastoma Staging System (Fig. 2). At 5 months of age, she developed bilateral cataracts and underwent cataract surgery, first on the left eye, followed by the right. Post-operatively, she developed pseudoptosis. Subsequently, she underwent anoplasty to correct anal stenosis, which had been diagnosed at 45 days of age, and recovered without complications. At 18 months of age, electroencephalography was performed due to an episode of abnormal body movements, although no epileptiform activity was detected. A brain ultrasound revealed normal supratentorial and infratentorial brain tissue, a normal ventricular system, and no evidence of space-occupying lesions, hydrocephalus, or midline shift (data not shown). She began walking at 18 months. At 20 months of age, an echocardiography indicated normal cardiac function, with no evidence of structural heart defects. At 23 months of age, magnetic resonance imaging of the entire spine demonstrated the loss of normal cervical lordosis, while lumbar lordosis was preserved (Fig. 3). At 26 months of age, imaging of the lower limbs revealed bilateral coxa vara with irregular distal femoral development, absent femoral epiphyses, bilaterally absent patellae and knock knees. At the age of 3 years, molecular genetic analysis was conducted using an EDTA blood sample.

All molecular genetic testing was conducted at an external center. The process was as follows: Peripheral blood leukocyte DNA was extracted following the protocol provided with a commercial DNA extraction kit (Thermo Fisher Scientific, Inc.) using genomic DNA. A NanoDrop spectrophotometer (Thermo Fisher Scientific, Inc.) was used to determine the concentration and purity of the extracted DNA, and the agarose gel electrophoresis was used to determine DNA integrity. Downstream genetic analysis was only done on high-quality DNA samples. Whole-exome sequencing was conducted to analyze the possible pathogenic variants in comprehensive genetic analysis. In the preparation of libraries, genomic DNA fragments of around 200-300 base pairs in size were prepared by fragmentation with an enzyme. The broken DNA was end-repaired, A-tailed and sequenced by ligation. The hybridization probes that targeted the human coding sequences were used to capture exonic regions and exon-intron boundaries. The amplified libraries were subsequently sequenced, and sequencing libraries were created. Next-generation sequencing was conducted on an Illumina Novaseq 6000 platform that produced paired end sequencing reads with a read length of 150 bp. sequencing on the target regions attained coverage depth of over 100x, which assured detection of single nucleotide variants, as well as, small insertions or deletions. A standardized bioinformatics pipeline was used to process raw sequencing data. Primary quality control was done to eliminate low-quality reads and sequencing adapters. The high-quality reads were then aligned to the human reference genome (GRCh37/hg19) with the help of a Burrows-Wheeler alignment program. Single-nucleotide variants and small insertions or deletions in coding regions were identified by performing variant calling. Annotations and filtering of the detected variants have been done according to allele frequency, predicted functional impact, and clinical relevance. Variability interpretation used data in publicly available databases such as ClinVar, gnomAD and the 1000 Genomes Project. Specific focus was placed on the LONP1 gene variants, which have been reported to be linked to CODAS syndrome. Determined variants were analyzed and categorized based on the criteria and principles of the American College of Medical Genetics and genomics as pathogenic, likely pathogenic, variant of uncertain significance, likely benign, or benign.

To confirm the candidate pathogenic variant identified through exome sequencing, a nested amplification of the identified genomic region was done by polymerase chain reaction. The products of the PCR were purified and submitted to confirmatory sequencing using Sanger Sequencing. The obtained chromatograms were compared and decoded against the reference sequence to establish the presence and zygosity of mutation identified. The last molecular diagnostic report contained the identified variant, the location on the genome, the anticipated pathogenicity, the mode of inheritance, and the association with the clinical presentation of the patient.

The patient was diagnosed with CODAS syndrome due to a homozygous Lon peptidase 1 (LONP1) gene variant (NM_004793.4 c.2008G>T; p. Ala670Ser). Additionally, a heterozygous variant was identified in the AGL gene (NM_000642.3 c.3837-1G>A, IVS28-1G>A; ClinVar ID:

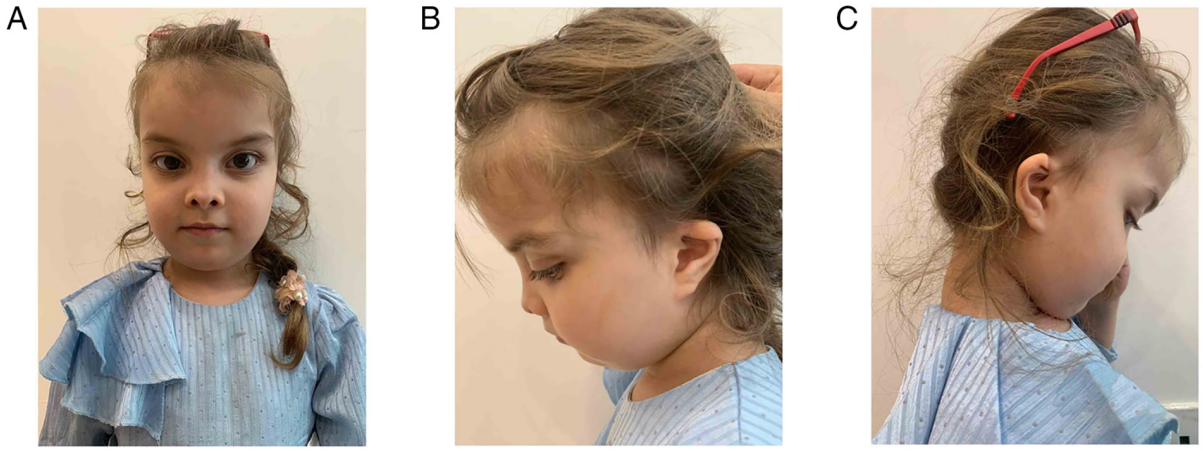

Figure 1. (A) The facial features of the patient include anteverted nares and misaligned eyes, (B) a crumpled left ear, and (C) a crumpled right ear.

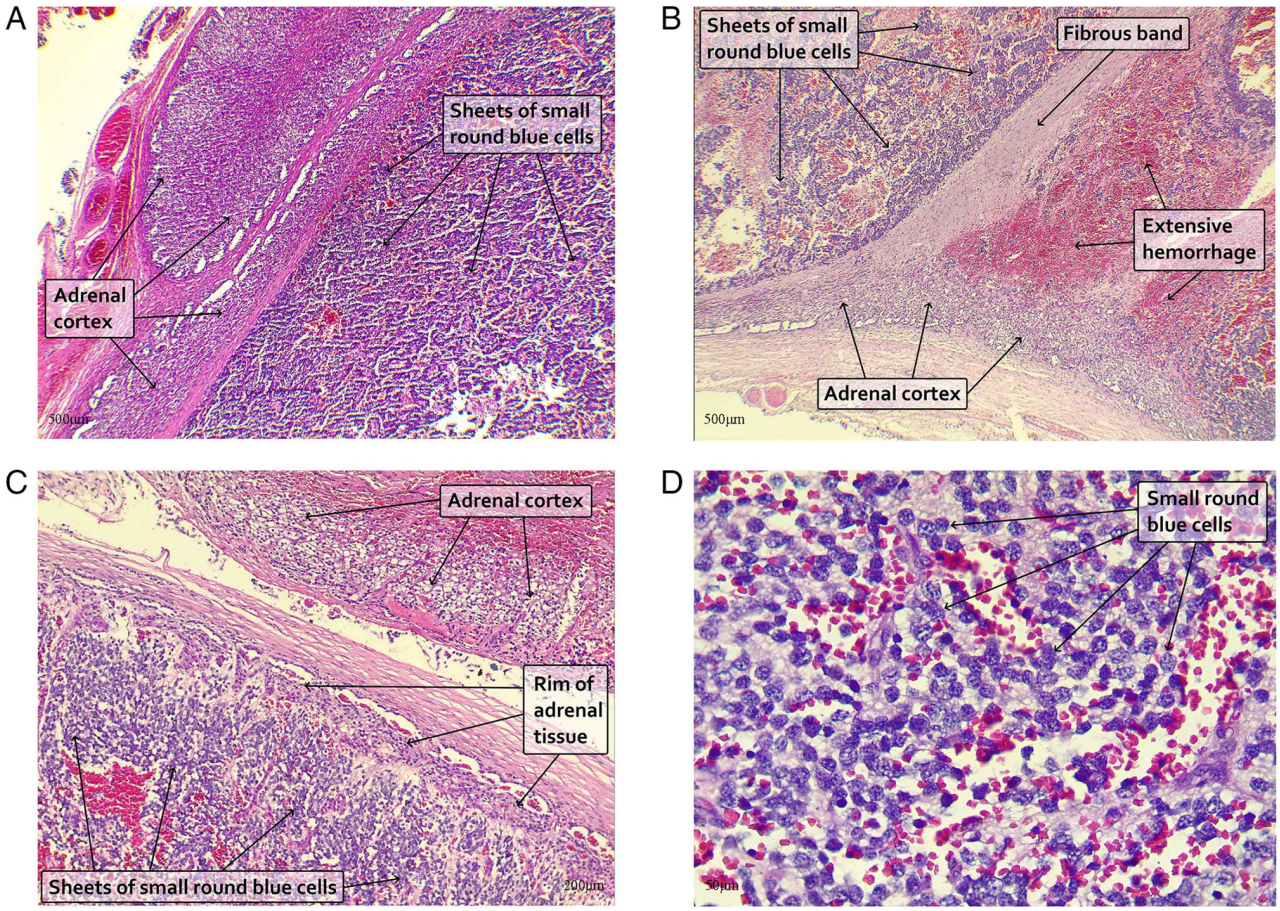

Figure 2. (A) The adrenal cortex lies adjacent to the tumor, composed of sheets of small round blue cells with a fibrous capsule and hemorrhage. (B) The sheets of tumor cells are separated by fibrous bands and show extensive hemorrhage. (C) Zones of the adrenal cortex can be seen adjacent to the sheets of small round blue cells. (D) The tumor cells have a small amount of amphophilic cytoplasm and medium-sized pleomorphic nuclei with irregular nuclear outlines, some being hyperchromatic and the others having vesicular chromatin with conspicuous nucleoli. (A-D) The images show hematoxylin and eosin staining; original magnification: (A and B) x40, (C) x100, (D) x400. The scale bars are as follows (A and B) 500 μm, (C) 200 μm, (D) 50 μm.

635291), associated with glycogen storage disease type III. A heterozygous variant in the MMUT gene (NM_000255.4 c.1466T>A; p. Val489Glu; rs747558018) was also detected, linked to methylmalonic aciduria, mut (0) type. As regards her renal abnormalities, an abdominal ultrasound revealed bilateral grade 1 hydronephrosis suggestive of vesicoureteral reflux (data not shown). Intravenous urography demonstrated left-sided hydronephrosis with a double collecting system and a dilated ureter extending to the bladder insertion. A voiding cystourethrogram indicated normal bladder capacity, grade 2 vesicoureteral reflux on the right side, and grade 3 vesicoureteral reflux on the left side. A urodynamic analysis

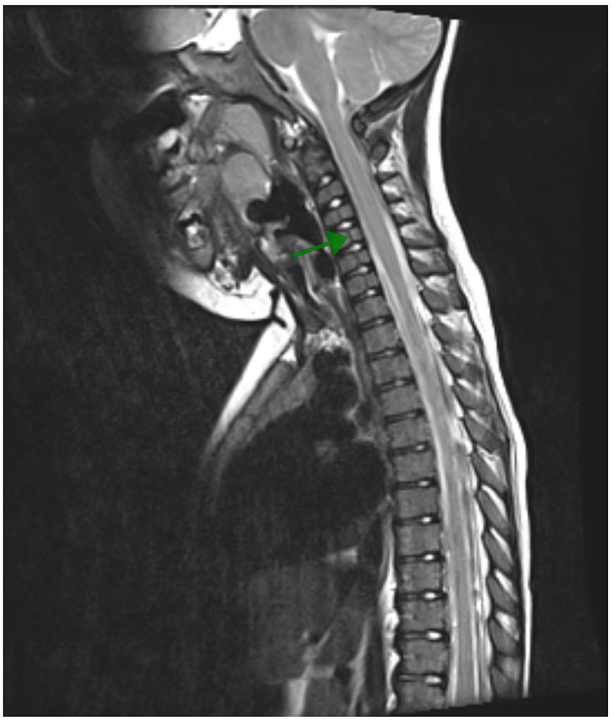

Figure 3. Cervical spine magnetic resonance imaging, T2 sagittal section, shows vertebral coronal defect and linear vertical hyperintensities in all cervical vertebral bodies (green arrow).

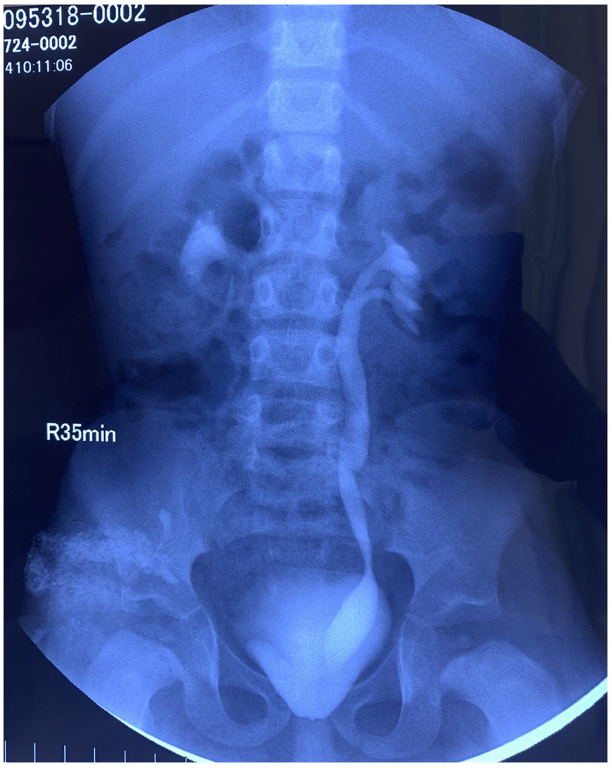

Figure 4. Intravenous urography shows a bifid collecting system of the left kidney, dilated left ureter down to the uretero-vesical junction, and normal excretion of the right kidney with no ureter dilatation.

revealed normal filling pressure, absence of detrusor overactivity, and no urine leakage with cough or Valsalva maneuver, but a small bladder capacity. Renal cortical imaging using dimercaptosuccinic acid revealed reduced cortical functional tissue in the right kidney, with differential renal cortical function measured at 34% on the right side and 66% on the left (Fig. 4). The patient is currently under physical rehabilitation therapy and observation.

Discussion

CODAS syndrome is a rare autosomal recessive disorder arising from bi-allelic mutations, either homozygous or compound heterozygous, in the LONP1 gene. This gene encodes Lon protease, a multifunctional mitochondrial enzyme that plays several critical roles: i) Removing misfolded and oxidatively damaged proteins; ii) facilitating the chaperone-like assembly of protein complexes within the respiratory chain; iii) mitochondrial gene expression regulation. Mutations in LONP1 disrupt mitochondrial homeostasis and lead to diverse clinical manifestations commonly associated with mitochondrial disorders. Different allele combinations that modify Lon function are considered to contribute to the variable presentation of CODAS syndrome symptoms (4). In mouse models, the homozygous loss of Lon was previously demonstrated to result in embryonic lethality, characterized by impaired growth and a reduced mitochondrial DNA (mtDNA) copy number, underscoring the essential role of the protein in mammals (11). By contrast, heterozygous mice developed similarly to wild-type counterparts. Together with the enzymatic study by Strauss *et al* (6), these findings suggest that the allele combinations associated with CODAS syndrome must alter, rather than entirely abolish, Lon function (4,6). In the study by Strauss *et al* (6), functional analyses revealed that these pathogenic mutations impair substrate-specific ATP-dependent proteolysis in mitochondrial proteostasis. Specifically, the LONP1 variant c.2161C>G (p.Arg721Gly) displayed impaired homo-oligomerization *in vitro*. Lymphoblastoid cells derived from affected individuals exhibited mitochondrial abnormalities, including swollen mitochondria with electron-dense inclusions, distorted inner membrane morphology, aggregated mtDNA-encoded cytochrome C oxidase subunit II, and a reduced respiratory capacity (6).

Cases of CODAS syndrome have been reported in individuals from diverse backgrounds, including Amish-Swiss in the USA (6), Mennonite-German in Canada (1,10), and Brazilian (5,7), Moroccans (9), as well as in Asian populations such as Saudi Arabia, Japan, Korea and China (2-5,8), highlighting its wide distribution. Despite this, CODAS syndrome remains exceedingly rare, with limited number of cases reported over the past 20 years (2,3,5,6,8). This may be attributed to one of two main explanations: Either the syndrome is extremely rare, or many cases lack the distinctive features needed for definitive diagnosis (5). A summary of cases of CODAS syndrome is presented in Table I.

The clinical spectrum of CODAS syndrome varies significantly, which complicates diagnosis. Some patients display only mild skeletal or ocular symptoms, lacking enough of the distinctive features necessary for a definitive diagnosis, while others exhibit additional malformations that further obscure identification. This variability and rarity of the disease pose challenges for establishing a clear genotype-phenotype correlation, and the exact molecular mechanisms by which LONP1

Table I. Summary of 15 cases of CODAS syndrome identified in the literature.

Ethnicity	Sex/age (years)	P.C	Mutation	Abnormalitie							(Refs.)
				Cerebral/CNS	Ocular	Dental	Auricular	Skeletal	Facies	Other	
Chinese	M/3	-	Heterozygous LONP 1 (p.A670V and p.R672C)	Speech delay, dysarthria, attention and learning difficulties	No eye contact, cCataract, nystagmus	Caries	Small and folded auricles	Valgus deformity, cracked femoral epiphysis	N/A	N/A	(2)
Saudi Arabian	F/1	-	Homozygous LONP 1 (p. Arg755Gly)	Microcephaly, Periventricular leukomalacia, dandy walker syndrome, mild mental retardation, epilepsy, delayed milestones	No eye contact	N/A	N/A	Developmental delay	N/A	N/A	(3)
Korean	M/10	-	LONP 1 (E476A; P749S)	Speech delay, dysarthria, attention and learning difficulties, delayed milestones, cerebellar atrophy	No eye contact, cataracts, strabismus, nystagmus	Caries	N/A	Truncal ataxia, posture instability, genu valgum, anterior pelvic tilt, lumbar hyperlordosis	Flat nose, anteverted nares	Jaundice	(4)
	F/6	-	LONP 1 (E476A; P749S)	Cerebellar atrophy, delayed milestones	Cataracts	Caries	N/A	Epiphyseal dysplasia, posture instability, genu valgum	N/A	Rhinitis and vitiligo	(4)
Japanese	M/12	-	Heterozygous LONP 1 (p.(Ser100Glnfs*46)), (p.(Arg786Trp)) .	Seizures, cerebellar atrophy	Cataracts	N/A	N/A	Short stature, spasticity of lower extremities, choreoathetotic movement, Epiphyseal dysplasia	N/A	Imperforate anus, rectovesical fistula, swallowing difficulties, hypotonia	(8)

Table I. Continued.

Ethnicity	Sex/age (years)	P.C	Mutation	Abnormalitie							
				Cerebral/CNS	Ocular	Dental	Auricular	Skeletal	Facies	Other	(Refs.)
Korean	F/5	-	Heterozygous LONP 1 (P749S; G767E)	Delayed milestones, intellectual disability, cerebellar hypoplasia	Cataracts	N/A	Crumpled ears	Epiphyseal hypoplasia and delayed ossification, genu valgus	Flat face, grooved nasal tip	N/A	(5)
Korean	M/4	-	Heterozygous LONP 1 (E476A; P749S)	Delayed milestones, intellectual disability, cerebellar hypoplasia	Cataracts	N/A	Crumpled ears	Epiphyseal hypoplasia and delayed ossification, genu valgus	Flat face, grooved nasal tip	N/A	(5)
Korean	F/3.5	-	Heterozygous LONP 1 (E476A; P749S)	Delayed milestones, intellectual disability	Cataracts	N/A	N/A	Subluxation of hips, Epiphyseal hypoplasia and delayed ossification	Flat face	N/A	(5)
Turkish	M/3	+	Heterozygous LONP 1 (A670V; I927del)	N/A	Cataracts	N/A	N/A	Epiphyseal hypoplasia and delayed ossification, genu valgus	Flat face	N/A	(5)
Turkish	M/8	+	Homozygous LONP 1 (R672C; R672C)	N/A	Cataracts	N/A	N/A	Epiphyseal hypoplasia and delayed ossification, genu valgus	Flat face	N/A	(5)
Brazilian	F/2.5	-	Homozygous LONP 1 (A670V; A670V)	Delayed milestones, Intellectual disability	Cataracts	N/A	Crumpled ears	Short stature, Subluxation of hips, Epiphyseal hypoplasia, and delayed ossification, vertebral coronal clefts	Flat face, grooved nasal tip	Laryngomalacia, congenital heart defect, tibial hemimelia, umbilical hernia	(5)

Table I. Continued.

Ethnicity	Sex/age (years)	P.C	Mutation	Abnormalitie							(Refs.)
				Cerebral/CNS	Ocular	Dental	Auricular	Skeletal	Facies	Other	
Moroccan	M/5	+	N/A	Moderate mental retardation	Cataracts, bilateral ptosis	Delayed tooth eruption, enamel dysplasia, decayed teeth	N/A	Hips dislocation, delayed epiphyseal ossification	Hyperteloris m, grooved nasal tip, flat face	Pharyngo-malacia, laryngomalaci a, laryngeal palsy, ureter dilatation, ventricular septal defect with pulmonary hypertension, cholestasis, hepatomegaly	(9)
Mennonite-German	M/2.5	-	N/A	N/A	Cataracts, ptosis	Unusual cuspal projections	Crumpled ears	Short humerus, delayed bone age, developmental delay	Grooved nasal tip	N/A	(10)
Brazilian	F/5	-	N/A	Developmental delay	Cataracts	Cusp tip extensions	Crumpled ears	Short stature, delayed bone age, very small radial and femoral epiphyses	Anteverted nares, flat nose	Hypotonia, mild pectoralis major hypoplasia	(7)
Mennonite-German	F/3	-	N/A	Microcephaly	Ptosis, cataracts	Delayed tooth eruption and unusual shape of teeth, anomalous cusps	Crumple ears	Hips dislocation, lumbar scoliosis, gena valga, pes valgus, short stature, delayed epiphyseal ossification, coronal clefts	Vertical groove on the nose tip	Hypotonia	(1)

M, male; F, female; P.C, parental consanguinity; -, negative; +, positive; N/A, non-available; CNS, central nervous system.

mutations lead to CODAS syndrome and its varied manifestations remain unclear (2,5,6,9). The multisystem effects of LONP1 mutations reflect a common theme in mitochondrial disorders, while the skeletal and dental abnormalities associated with CODAS syndrome are notably distinct and regarded as pathognomonic (3,6). In addition, the disease manifestation varies. Tang *et al* (2) reported the case of a Chinese boy with cognitive impairment, cataracts, dental anomalies, auricular malformations and skeletal abnormalities present from birth. Whole exome sequencing revealed a compound heterozygous missense mutation (NM_004793: c.2009C>T/p. A670V and c.2014C>T/p. R672C) in LONP1 (2). Yoo *et al* (4) reported the first familial cases of CODAS syndrome worldwide in two siblings, both carrying the LONP1 mutations E476A and P749S. This unique familial case indicates that specific allele combinations likely influence the severity and variability of CODAS symptoms (4). To the best of our knowledge, the present case report represents the first case of CODAS syndrome in Iraq. The patient was born at 34 weeks of gestation via cesarean section to two second-degree cousins. Her medical history included respiratory distress syndrome at birth, a left adrenal mass diagnosed as undifferentiated neuroblastoma at 2 months of age, bilateral cataracts, and a series of developmental and anatomical abnormalities. At 18 months, she began walking, and imaging at 23 months of age revealed spine and lower limb abnormalities, including bilateral coxa vara and absent femoral epiphyses. At 3 years of age, molecular genetic analysis identified CODAS syndrome, caused by a homozygous LONP1 gene variant (NM_004793.4 c.2008G>T; p. Ala670Ser). In addition, variants were detected in the AGL gene, associated with glycogen storage disease type III, and in the MMUT gene, linked to methylmalonic aciduria, mut(0) type. This case may represent the first reported instance of CODAS syndrome associated with a LONP1 mutation in the presence of two additional gene mutations. However, there is currently no definitive evidence supporting a contributory role of these additional mutations in the development or clinical manifestations of the syndrome. Investigations by future molecular studies may be warranted to clarify this association and to determine the potential contribution of the additional mutations to the pathogenesis of the syndrome.

An increasing body of evidence suggests that the upregulation of LONP1 is a common feature across multiple types of cancer, with an elevated expression reported in lymphoma, oral squamous cell carcinoma, colorectal cancer, cervical cancer, anaplastic astrocytoma, melanoma, glioblastoma and bladder cancer compared with normal, non-transformed tissues (12). Although a causal association between the LONP1 mutation and neuroblastoma development in the case described herein cannot be definitively established, further studies are required to clarify this potential association. In the present case report, the neuroblastoma may represent a congenital malignancy rather than a manifestation of CODAS syndrome, as renal abnormalities are not recognized as specific features of CODAS. Given that the patient was 4 years of age and that neuroblastoma predominantly occurs in early childhood, with ~90% of cases diagnosed before the age of 5 years (13). From a clinical management standpoint, CODAS syndrome poses challenges for pediatric neurologists and rehabilitation specialists, as effective genetic treatments are limited. Selecting appropriate gene therapies and determining their timing is difficult, and treatment primarily aims to alleviate symptoms based on limited case data. Encouraging physical activity and providing supportive therapies are recommended to enhance patients' quality of life and support their development into independent adults with societal roles (3). The patient whose case is described herein is currently under physical rehabilitation therapy and observation.

In conclusion, the present case report describes the first Iraqi case of CODAS syndrome, associated with a homozygous variant in the LONP1 gene (p. Ala670Ser). Additionally, heterozygous variants in the AGL gene (NM_000642.3 c.3837-1G>A, IVS28-1G>A; ClinVar ID: 635291) and in the MMUT gene (NM_000255.4 c.1466T>A; p. Val489Glu; rs747558018) have been detected, which warrants further investigation to reveal any association with the syndrome.

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Availability of data and materials

The data related to this report can be provided by the corresponding author upon reasonable request. The whole-genome sequencing dataset for this case was registered in the Sequence Read Archive (https://www.ncbi.nlm.nih.gov/sra/PRJNA1446893) with accession no. PRJNA1446893.

Authors' contributions

RB, RMA, SHT and FHK conceptualized the study. REM, RB, NHH, SHT, BMA and ATA were involved in analyzing the patient's data and in obtaining medical images. HOA, REM, BAM, RB, BMA and ATA, SMA, KMH, MSM, LAS and AKG were involved in the design and conceptualization of the study, in analyzing the patient's data and in obtaining medical images. HOA and SMA were involved in the writing of the original draft of the manuscript. KMH, MSM, AKG, BAM, FHK, BMA and ATA were involved in reviewing and editing of the manuscript. All authors have read and approved the final version of the manuscript. RB and NHH confirm the authenticity of all the raw data.

Ethics approval and consent to participate

Written informed consent was obtained from the patient's parents for participation in the present case report.

Patient consent for publication

Written informed consent was obtained from the patient's parents for publishing the present case report and the associated images.

Competing interests

The authors declare that they have no competing interests.

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