

Case Report

Cerebro-oculo-facio-skeletal syndrome: Clinical and genetic insights in a child with neuroregression

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ABSTRACT

Cerebro-oculo-facio-skeletal (COFS) syndrome is a rare autosomal recessive inherited disorder characterized by microcephaly, congenital cataracts and/or microphthalmia, arthrogryposis, developmental delay, and facial dysmorphism. It is now recognized as a disorder belonging to the spectrum of inherited defects in nucleotide excision repair. Hereby, we report a 13-month-old female, the second born of third-degree consanguineous marriage, who presented with neuroregression. She had microcephaly, nystagmus, bilateral congenital cataracts, hypotonia, and absent deep tendon reflexes. Neuroimaging showed diffuse hypomyelination of the bilateral cerebral white matter, suggesting hypomyelinating leukodystrophy. Whole exome sequencing revealed a homozygous pathogenic variant in exon 19 of the excision repair cross-complementation 2 gene, confirming COFS syndrome. So far, 14 cases described as COFS syndrome have been studied at the molecular level. This case highlights the importance of early recognition of neuro-regression alongside a systematic approach with early genetic evaluation to narrow down to the correct diagnosis. Given its rarity, this case report contributes significantly to the understanding of its clinical spectrum and potential management strategies.

Keywords: Cerebro-oculo-facio-skeletal syndrome, Congenital cataract, Hypomyelination, Neuroregression, Nucleotide excision repair.

INTRODUCTION

Cerebro-oculo-facio-skeletal (COFS) syndrome is a rare autosomal recessive neurodegenerative disorder within the spectrum of nucleotide excision repair (NER) defects. It is characterized by microcephaly, congenital cataracts, arthrogryposis, and progressive neurological deterioration.^[1] The condition represents the severe congenital end of deoxyribonucleic acid (DNA) repair disorders caused by pathogenic variants in excision repair cross-complementation 1 (ERCC1), ERCC2, ERCC5 and ERCC6, leading to accumulation of unrepaired DNA and subsequent neurodegeneration.^[2] Due to significant clinical overlap with other congenital neurodegenerative syndromes, COFS is frequently underdiagnosed or misclassified. Early recognition and genetic confirmation are essential, particularly in populations with high rates of consanguinity.

CASE REPORT

A 13-month-old female, born to third-degree consanguineous parents, presented with loss of previously acquired developmental milestones, failure to thrive and abnormal eye movements. Antenatal and perinatal histories were unremarkable. She was delivered at 38 weeks with intrauterine growth restriction (birth weight: 1.7 kg). There

was no history of fever, seizures, or perinatal asphyxia. The mother had two previous first-trimester miscarriages, and the father, also born of a consanguineous marriage, had two younger siblings who died in infancy due to suspected neurological illness.

Initially, the child exhibited global developmental delay, achieving head control at 7 months and sitting with support at 10 months. From 11 months of age, she developed neuroregression, with current development corresponding to approximately 6 months.

Examination revealed microcephaly, low-set ears, failure to thrive, hypotonia, with absent deep tendon reflexes, bilateral cataracts, micro-ophthalmia, and horizontal nystagmus. Magnetic resonance imaging (MRI) of the brain showed diffuse hypomyelination involving the bilateral cerebral white matter, internal capsule and subcortical regions, consistent with hypomyelinating leukodystrophy [Figure 1].

Congenital infections including toxoplasmosis, cytomegalovirus, rubella, syphilis, and herpes simplex virus were ruled out with appropriate investigations. Differential diagnoses considered were hypomyelination with congenital cataract syndrome, Pelizaeus-Merzbacher disease, and COFS

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syndrome. Whole-exome sequencing revealed a homozygous pathogenic variant in exon 19 of the *ERCC2* gene [c.1760 > T (p.Ala58Val)], confirming COFS syndrome type 2.

The patient received multidisciplinary supportive care focused on nutritional optimization, aspiration prevention, physiotherapy, genetic counseling, and regular follow-up. Cataract extraction was deferred due to poor visual prognosis.

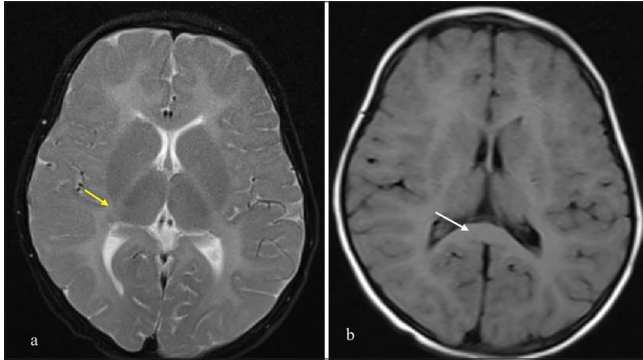


Figure 1: A 13-month-old female child, presenting with neuro-regression and congenital cataract, diagnosed as Cerebro-Oculo-Facio-Skeletal syndrome. (a) Magnetic resonance imaging (MRI) brain (Axial T2-weighted image) shows diffuse hypomyelination of bilateral cerebral white matter, internal capsule, and subcortical regions with relative preservation of cortical grey matter (yellow arrow). (b) MRI brain (Sagittal T1-weighted image) shows cerebral atrophy with thinning of the corpus callosum (white arrow), consistent with hypomyelinating leukodystrophy.

DISCUSSION

COFS syndrome, first described by Peña and Shokeir in 1974, remains exceedingly rare, with fewer than 50 reported cases and only a subset having molecular confirmation.^[1] The disorder encompasses a spectrum of *NER* gene defects (*ERCC1*–*6*), which play critical roles in DNA damage recognition and repair. Disruption of these pathways results in progressive cellular dysfunction and generalized neurodegeneration.^[3] As in our case, COFS syndrome typically presents with intrauterine growth restriction, microcephaly, micro-ophthalmia, optic atrophy, and characteristic facial dysmorphism. Congenital bilateral cataract is a key hallmark attributable to early lens fiber damage and opacification. Neurological features include profound developmental delay, spasticity, and neuroregression^[1-3]. Arthrogyposis occurs at the later stages.

MRI finding of diffuse hypomyelination is a key radiological indicator^[4] and, when accompanied by congenital cataracts and microcephaly, should prompt evaluation for COFS syndrome. The possible differential diagnoses for COFS syndrome include Hypomyelination-congenital-cataract syndrome, Pelizaeus–Merzbacher syndrome, Congenital Rubella syndrome, etc., which would warrant systematic exclusion based on the clinical pointers as mentioned in Table 1.

Among the four recognized subtypes, COFS syndrome type 2 (associated with *ERCC2* mutations) generally manifests with a severe neonatal phenotype.^[5]

Table 1: Differential diagnoses for cerebro-oculo-facial-skeletal syndrome.

Differential Diagnosis	Clinical pointers	Typical age of presentation	Diagnostic investigations
Hypomyelination with Congenital Cataract syndrome	Congenital cataracts, GDD, hypotonia.	Infantile	Magnetic resonance imaging (MRI) of the brain, genetic testing
Pelizaeus–Merzbacher disease	Nystagmus, Hypotonia, Ataxia, Developmental delay, Absence of cataracts.	6 months–2 years	MRI Brain, genetic testing, nerve conduction study.
Mitochondrial disorders (e.g., Leigh syndrome, mitochondrial cytopathies)	Neuroregression, hypotonia, seizures, lactic acidosis, ophthalmologic abnormalities	Infancy–early childhood	Serum/CSF lactate and pyruvate, MRI brain, mitochondrial gene panel
Lowe syndrome (oculocerebrorenal syndrome)	Congenital cataract, hypotonia, neurodevelopmental delay, Renal–Fanconi syndrome	Infancy–early childhood	Urine amino acids, low-molecular-weight proteinuria, <i>OCRL</i> gene testing
Congenital rubella syndrome	Congenital cataract, microcephaly, hearing loss, developmental delay, cardiac defects	At birth	Rubella IgM and Rubella IgG
Smith–Lemli–Opitz syndrome	Congenital cataract (occasionally), hypotonia, syndactyly, genital anomalies, and neurodevelopmental delay	Birth–infancy	Serum 7-dehydrocholesterol, <i>DHCR7</i> gene testing.
Peroxisomal Disorders (e.g., Zellweger spectrum)	Hypotonia, seizures, dysmorphic facies, abnormal eye findings including cataracts, liver dysfunction	Neonatal period	Very long-chain fatty acids, <i>PEX</i> gene testing

GDD: Global developmental delay, CSF: Cerebro spinal fluid, IgM: Immunoglobulin M, IgG: Immunoglobulin G

Although many ERCC2 variants are documented in related NER disorders, such as xeroderma pigmentosum, trichothiodystrophy, and Cockayne syndrome, the ERCC2 variant identified in our case has not been reported previously, thereby expanding the known genotypic spectrum of COFS syndrome type 2. The above table enlists the possible differential diagnoses for COFS syndrome, describing the common clinical features along with their age of presentation and diagnostic investigations.

COFS syndrome is rapidly progressive and frequently fatal in early childhood. Most affected children succumb to respiratory infections secondary to feeding difficulties, typically within the first 5 years of life. The mean age of death is approximately 3.5 years.^[6] Despite this, our patient with a novel ERCC2 variant demonstrated a comparatively milder phenotype and late clinical presentation.

CONCLUSION

In any child presenting with congenital cataract, neuroregression and hypomyelinating leukodystrophy, COFS syndrome should be considered as a differential diagnosis. Early identification through neuroimaging and genetic evaluation facilitates timely diagnosis, appropriate supportive care and counseling.

Ethical approval: Institutional Review Board approval is not required.

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given consent for their images and other clinical information to be reported in the journal. The patient understands that the patient's names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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