Navigating the rare : A case report of Angelman syndrome coexisting with oculocutaneous albinism

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Abstract

Abstract: An association of oculocutaneous albinism with Angelman syndrome is a rare entity. Here, we discuss about a four year old male child born with classic albino features. He presented to us at nine months of age with genetically proven OCA2, Global developmental delay and seizures. As the child had refractory seizures and very slow response to multidisciplinary therapy, he was suspected to have a dual pathology and hence specific genetic testing for Angelman syndrome was done which helped to have greater clinical insight into his special challenges.

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- Angelman syndrome
- Oculocutaneous albinism
- Global development delay
- Autism spectrum disorder

Introduction

Oculocutaneous albinism (OCA) refers to a rare group of genetically diverse disorders inherited in an autosomal recessive manner, caused by mutations in genes involved in melanin production. Individuals with OCA typically present with various eye-related issues, including nystagmus, reduced vision, light sensitivity, strabismus, underdevelopment of the fovea, light-colored irises, and difficulties with color perception. [(1)] The severity of OCA symptoms can differ widely—from partial reduction in skin and hair pigmentation to a complete absence of melanin, primarily linked to disruptions in tyrosine metabolism. So far, seven subtypes of OCA (OCA-7) have been identified, with OCA2 being the most prevalent. Notably, about 1% of individuals with Angelman or Prader-Willi syndromes also exhibit OCA2.

Angelman syndrome (AS) is a complex neurodevelopmental disorder characterized by impaired motor coordination, significant speech delay, intellectual disability, and distinct dysmorphic features. [(2)] The condition arises from the loss of function of the *UBE3A* gene, which encodes a ubiquitin-protein ligase E3A, located on chromosome 15. This gene is typically maternally expressed in neurons, and its dysfunction leads to abnormalities in neuronal signaling, synaptic development, and neural plasticity. Clinically, AS is associated with microcephaly, absent or severely limited verbal communication, a characteristic happy demeanor with frequent smiling or laughter, stereotyped or autistic-like behaviors, ataxic gait, and epilepsy. [(3)] Seizures in AS are often refractory and usually require treatment with broad-spectrum antiepileptic medications. [(4)]

Case Report

A 9 months old boy born of spontaneous conception to a nonconsanguineous couple at maternal age of 30 and paternal age of 35 at time of conception, was brought with complaints of developmental delay and recurrent seizures. Mother had no history of earlier pregnancy losses. Double marker test, nuchal translucency and anomaly scan were normal. Mother had history of hypothyroidism and pregnancy induced hypertension managed with medications. Pregnancy was terminated at 35 weeks of gestation following preeclampsia. Baby had good apgar at birth and had albino features - blond hair with pale skin and eyelash. He was admitted in NICU on Day 01 of life in view of prematurity, low birth weight (1.6kg) and recurrent seizures requiring two anti-seizure medications- Phenobarbitone and levetiracetam. Neurosonogram and metabolic screening during neonatal period was normal. He was discharged on day 07 of life on anti-seizure medications and parents were counselled for high risk follow up and development surveillance.

At 09 months he had microcephaly, squint, horizontal nystagmus, generalised hypertonia with only partial neck control and not rolling over. Ophthalmologic evaluation showed iris heterochromia, hypopigmented retina and foveal hypoplasia. He was initiated on intense development therapy sessions, seizure medications and muscle relaxants. Meanwhile he continued to have multiple episodes of seizures requiring add on medications. Despite intensive continuation of multidisciplinary therapy his developmental age remained almost static.

At three years of age he continued to have no verbal output, dystonic movements with hand manipulation, mannerism and restricted socialisation. Hearing evaluation was normal. Modified Checklist for Autism in Toddlers assessment at 3 years of age was 11 showing high risk for Autism Spectrum Disorder (ASD). At four years of age his CARS score was 32 showing mild to moderate ASD. REELS assessment showed receptive and expressive language age less than six months. Development assessment with DDST II showed gross motor age of 15 months and fine motor, expressive language and social milestones corresponding to 09 months.

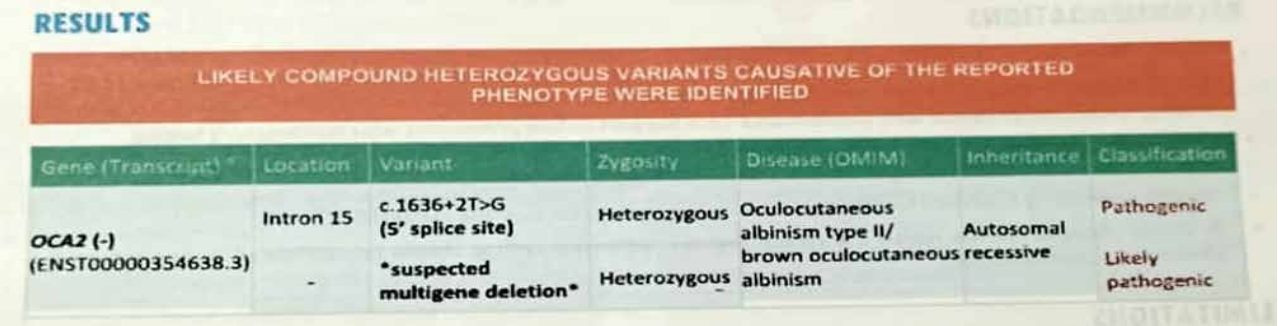
At four years he was diagnosed as Global developmental delay (Development quotient -22) and non verbal Autism Spectrum Disorder (Fig 3). Repeat EEG showed continuous burst of generalised epileptiform activity and suppression which was suggestive of epileptiform encephalopathy.

As the seizures were refractory with global development delay and a happy demeanour Angelman Syndrome was clinically suspected and genetic analysis was done (Fig 2, Fig 3). Results of PWS DNA methylation analysis was pathognomic for Angelman syndrome. Parents were counselled about the long term need of intensive autism appropriate therapy along with physical rehabilitation He is enrolled into special school. His seizures are controlled on two anti-seizure medications-sodium valproate and clobazam.

Figure 1: Phenotypic presentation in a case of Angelman syndrome with oculocutaneous albinism

Discussion

While case reports have established a connection between hypomelanotic disorders such as tuberous sclerosis and autism, cases involving albinism are rare. Raj G et al. (2022) reported a case involving a three-year-old female child presenting with low birth weight, a history of neonatal intensive care unit (NICU) admission, and developmental delays in fine motor skills, social cognition, and language. The child also exhibited hyperactivity, socially inappropriate behaviors, limited eye contact, and a preference for solitary play. [5] Ophthalmologic evaluation revealed foveal hypoplasia, leading to a diagnosis of oculocutaneous albinism. Another

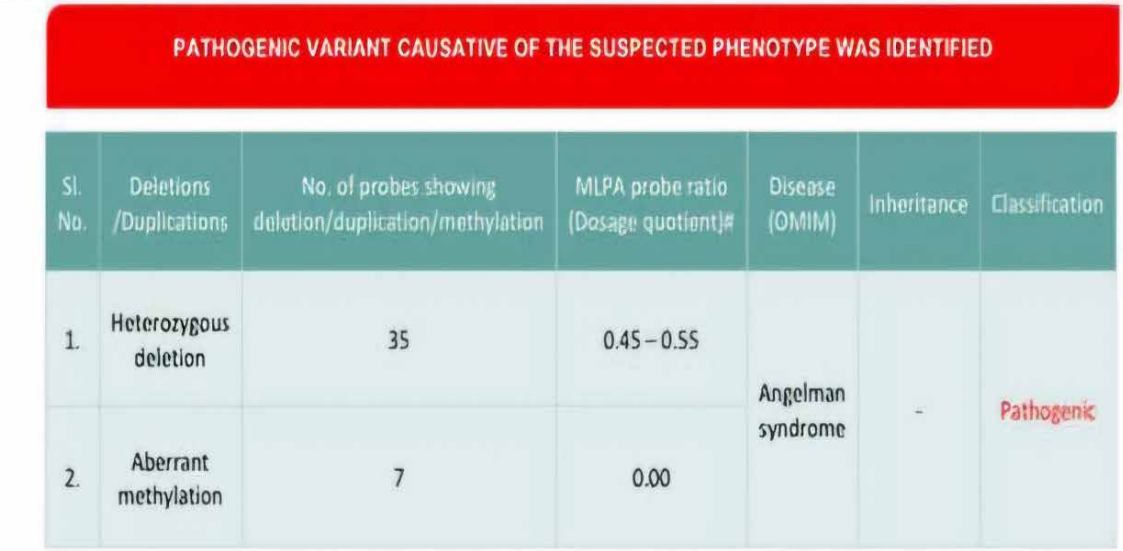


RESULTS

LIKELY COMPOUND HETEROZYGOUS VARIANTS CAUSATIVE OF THE REPORTED PHENOTYPE WERE IDENTIFIED

Gene (Transcript) *	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
OCA2 (-) (ENST00000354638.3)	Intron 15	c.1636+2T>G (5' splice site)	Heterozygous	Oculocutaneous albinism type II/ brown oculocutaneous albinism	Autosomal recessive	Pathogenic
	-	*suspected multigene deletion*	Heterozygous			Likely pathogenic

Figure 2 :Genetic study revealing OCA2 pathogenic variant of oculocutaneous albinism type II



PATHOGENIC VARIANT CAUSATIVE OF THE SUSPECTED PHENOTYPE WAS IDENTIFIED

Sl. No.	Deletions /Duplications	No. of probes showing deletion/duplication/methylation	MLPA probe ratio (Dosage quotient)#	Disease (OMIM)	Inheritance	Classification
1.	Heterozygous deletion	35	0.45 – 0.55	Angelman syndrome	-	Pathogenic
2.	Aberrant methylation	7	0.00			

Figure 3 :Genetic study revealing Angelmann syndrome

study was reported by Chaitanya Varma et al (2023) describing association between OCA and ASD pointing out a genetic relationship between OCA and ASD.

The association between oculocutaneous albinism with autism has been rarely reported in literature. In a case report by Yurie Fukiyama et al (2018) at Osaka, a similar presentation was noted which aligns with our findings.[6] Another case report was reported by Chinese literature , Zhou QJ et al (2023) showing genetic relationship and complications associated with a combination of OCA 2 mutation with Angelman syndrome.[7] To the best of our literature reaserch there have been no reported case studies from India to date.

Since refractory seizures are uncommon with OCA , further evaluation helped us identify the coexisting Angelman syndrome. Most patients with epilepsy are diagnosed as AS following their diagnostic EEG patterns as reported by Ranasinghe JC et al. Patients with Angelman syndrome may experience both provoked and unprovoked seizures. Epileptic manifestations tend to be more severe in individuals with a deletion involving the 15q11–q13 chromosomal region.

CONCLUSION

Diagnosing AS early is a challenging due to nonspecific symptoms and increase chance of misdiagnosis with other common genetic condition.[8]AS should be taken into account in the differential diagnosis of infants with delayed developmental milestones, seizures, especially in children with happy facies and ocular abnormalities like strabismus. Though oculocutaneous albinism in a child with Angelman syndrome is only 1%, it must also be considered during evaluation process. Vision correction, proper stimulation, intensive speech and physiotherapy must be started early.

An earlier diagnosis will help clinicians to foresee complications, better compliance and coperation with treatment plan. Hence high index of suspicion and earlier genetic diagnosis will help decrease ambiguity and enable clearer decision making hence improving overall patient outcome.

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