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Case Report

Oral Clinical Features and Dental Management of Alazami Syndrome. Case Report

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ABSTRACT

Alazami Syndrome is a rare autosomal recessive genetic disorder caused by biallelic pathogenic mutations in the La Ribonucleoprotein 7 gene, initially identified in a Saudi consanguineous family in 2012. This syndrome presents diverse clinical features, including significant growth restriction, intellectual disability, and distinctive facial characteristics, which contribute to its diagnostic profile. Patients with Alazami Syndrome commonly display severe intellectual disability, growth retardation manifesting as primordial dwarfism, and characteristic facial traits such as a triangular-shaped face, prominent forehead, and dental malocclusion. Additional clinical findings may include microcephaly, skeletal anomalies, thickened skin, and neurobehavioral abnormalities, including hypersensitivity to sensory stimuli and autistic-like behaviors. This case report aims to detail the oral clinical features and specific dental management approaches for a patient with Alazami Syndrome, highlighting the challenges and considerations in providing comprehensive care. The findings provide insights into the dental care needs of patients with Alazami Syndrome and underscore the importance of a multidisciplinary approach for optimal patient outcomes.

Keywords: AlAzami, case report, dental, rehabilitation, Saudi Arabia

Introduction

Alazami Syndrome is a rare genetic disorder inherited in an autosomal recessive manner and caused by biallelic pathogenic mutations in La Ribonucleoprotein 7 (LARP7). It was first described by Alazami *et al.* in 2012 in a Saudi consanguineous family.[1] Alazami syndrome presents various clinical characteristics and exhibits variability within families and across different patient populations.[2]

Based on the published documented case reports, the Fundamental clinical features of Alazami Syndrome are the following.

Individuals with Alazami Syndrome experience significant growth retardation, evident in both height and weight, often falling multiple standard deviations below the age-adjusted mean.[1-8] This growth delay is usually present from birth, categorizing Alazami Syndrome as primordial dwarfism.[1-3,6,7,9] However, the severity of growth restriction can vary, with some individuals exhibiting a less pronounced deficit in height compared to others.[2,6,9]

Severe intellectual disability is a hallmark of Alazami Syndrome, universally observed in all reported cases.[4,7] This manifests as severely delayed or absent speech, inability to follow commands, and challenges recognizing familiar individuals.[2,6-8,10,11]

Alazami Syndrome patients often display a characteristic pattern of facial features, which can aid in diagnosis. These include the triangular-shaped face, prominent forehead, deep-set eyes, broad nose, malar hypoplasia, wide mouth, full lips, dental malocclusion, or widely spaced teeth.[1,2,5,7-9,11] Furthermore, the literature reveals a spectrum of additional findings and variability in the clinical presentation of Alazami Syndrome: microcephaly is frequently reported in Alazami Syndrome, it is often disproportionately mild relative to the severity of growth restriction.[1,4-7,9,10] Some patients may even have a normal head circumference, distinguishing Alazami Syndrome from other microcephalic primordial dwarfism disorders.[2] Skeletal findings in Alazami Syndrome can include slender long bones with increased cortical thickness,[1,2,8-10] proximally placed fourth toes and thumbs,[2,9] scoliosis, short distal phalanges and nails, a thin calvarium with a low-density skullcap, and fingerprint marks on skull X-rays.[1,2,4,5,7-9] Thickened skin over the hands and feet, noted as a potentially recognizable sign, Cutis marmorata, and streaky

hyperpigmentation.[2,3,5,7] Behavioral abnormalities are frequently associated with Alazami Syndrome, contributing to its complexity of presentation. These can include severe anxiety, hypersensitivity to stimuli such as touch and sound, stereotypic handwringing, resembling movements observed in Rett Syndrome,[2] autistic-like behaviors, including repetitive movements and limited social interaction,[9] temper tantrums, and agitation.[3,7]

Additional findings reported in some Alazami Syndrome patients include small kidneys,[3,5,8] pre-hypertension, ocular abnormalities, such as strabismus, keratoconus, vision impairment, atrial septal defects, seizures, and hypotonia.[1,2,4,5,8] Moreover, several other aspects of variation in Alazami Syndrome have been reported based on different presentations across different populations: Alazami Syndrome was initially described in families with consanguinity, and cases are now being identified in individuals without this history.[4,8] The prevalence of Alazami Syndrome may be higher in populations where consanguineous marriages are more common.[1,6,10,11] Alazami Syndrome has been reported in individuals from diverse ethnic backgrounds, suggesting it is not restricted to any specific population. Cases have been documented in individuals of Saudi Arabian, Jordanian, Afghani, Caucasian/Northern European, Algerian, Spanish, and Japanese descent.[1,2,4,5,7-9,11] The specific mutations in the *LARP7* gene may contribute to the variability in Alazami Syndrome presentation. The sources detail various types of mutations, including homozygous frameshift mutations, compound heterozygous mutations (two different mutations in the *LARP7* gene), and deletions affecting splice sites.[1,6,7,9] These mutations lead to different levels of LARP7 protein dysfunction, potentially influencing the severity and specific features of Alazami Syndrome.[2,9,12]

Alazami Syndrome is considered a rare disorder. Less than thirty-five cases have been reported until now,[12] and to our knowledge, it has not yet been reported from oral and dental perspectives. This report followed the reporting guidelines of case reports (CARE),[13] aiming to present a case of Alazami Syndrome in a female consanguineous Saudi family, emphasizing oral and dental characteristics and management.

Case Report

The case presents a female patient born on 15 December 2015 and referred to the pediatric dentistry department of Khamis Mushait Maternity and Children's Hospital in Aseer Region, Saudi Arabia, by an endocrinologist with the chief compliant short stature. Signs and symptoms: poor weight gain, decreased cognitive function, delayed speech, developmental delay, strabismus. The celiac profile was negative. However, the whole exome sequencing (WES) reported on 23 May 2024 (Table 1) revealed a pathogenic homozygous frameshift mutation in gene LARP7, and the supportive phenotype of the patient confirmed a genetic diagnosis of Alazami Syndrome.

This variant has been described in the literature as a causative of a neurodevelopmental disorder (PMID: 32552793, 26607181, 22865833). It is not in general population databases (gnomAD: no frequency, dbSNP: rs1057519017). This sequence change is a duplication of seven nucleotides (c.1024_1030dup), which would cause a frameshift in the protein's reading frame and alter the amino acid sequence beginning at codon 344. Therefore, this variant is expected to result in an absent or disrupted protein product. Loss-of-function variants in *LARP7* are known to be pathogenic (PMID: 22865833, 26374271, 26607181). Based on the available information, this variant is pathogenic.

Bi-allelic pathogenic variants in *LARP7* cause Alazami Syndrome (ALAZS). The patient is characterized by severe growth restriction that resulted in a short stature or primordial dwarfism. The patient manifests severe intellectual disability and distinct facial features, including malar hypoplasia, deep-set eyes, strabismus, broad nose, short philtrum, and macrostomia. The patient has no specific skeletal findings (Table 2).

Clinical findings

Upon oral and dental examination, the patient has widely spaced upper anterior teeth. The patient has crowded lower anterior teeth due to retained primary teeth. Moreover, the dental caries was found as smooth surface dental caries in teeth #63 #73 #83 (Figure 1).

Radiographic assessment

Upon radiographic examination, the patient showed taurodontism of the first permanent molars. Although the orthopantomograph was not ideal due to the behavior challenge, it was not repeated to not expose the patient to unnecessary radiographic doses (Figure 2).

Dental intervention

Due to the behavior challenges with the patient, preventive treatment (fissure sealant for all permanent

Table 1: Summary of variant (s) identified as the most relevant to the described phenotype of the patient

Gene & (transcript)	cDNA change	Amino acid change	Molecular consequence	Zygosity	MAF*	Classification & (CADD** score)	OMIM phenotype & (inheritance)
LARP7 (NM_016648.4)	c. 1024_1030dup	p.Thr344fs	Frameshift	Homozygous	0%	Pathogenic (29.7)	Alazami Syndrome (AR)

*MAF: Minor allele frequency; based on gnomAD data. **(Deleterious: ≥20, Likely Deleterious: 10–19, Unlikely Deleterious: <10)

Table 2: The patient's phenotypic features description

Age	8 years–10 months
Weight (Kg)	12.7
Height (cm)	104.5
Face	Triangular-shaped face
Eyes	Deep-set eyes, narrow palpebral fissures, and blue sclera
Hear	Appear normal
Head	A prominent forehead and microcephaly
Thyroid gland	Hyperthyroidism
Heart	No abnormality detected
Hematological	In the expected normal range
Renal Ultrasound	Common renal morphology and function
Gastroentetistinal examination	Taking well orally

molars and fluoride varnish application) and the extraction of the retained or near to exfoliated primary teeth (teeth #54 #53 #64 #63 #73 #72 #83 #82 #81) were decided to be done under general anesthesia, which was held in the day surgery unit and the patient discharged home after the surgery.

Follow-up and anticipatory guidance

In the follow-up visit after 1 week, the patient's family reported no complications after treatment. They have been informed about the importance of regular dental checkups and given appointments accordingly. The follow-up program will follow the anticipatory guidance to address the patient's needs aligned with her age, including oral hygiene practices, oral/dental development and growth, speech/language development, diet and nutrition, and injury prevention.

Discussion

This report can shed light on new dental literature since it is, up to my knowledge, the first report of the Alazami Syndrome from the oral and dental literature. The behavioral and intellectual abilities of the patient challenged the diagnostic intervention, the radiographs, especially. Moreover, this report is consistent with the scarce published literature about the Alazami Syndrome in terms of the general phenotypic features. This necessitates the importance of the comprehensive diagnostic approach through detailed clinical evaluation, a thorough assessment of growth, developmental

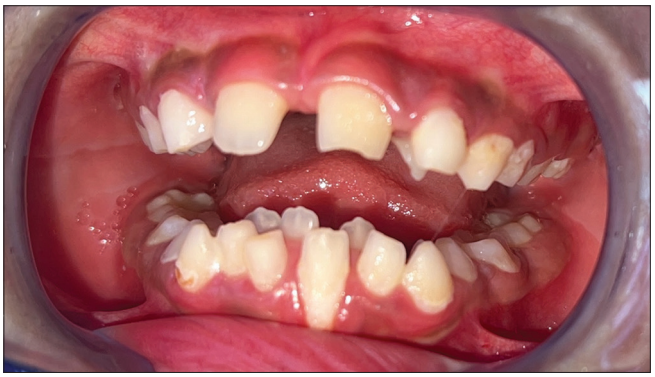

Figure 1: Intraoral photograph shows widely spaced upper anterior teeth and crowding of lower anterior teeth

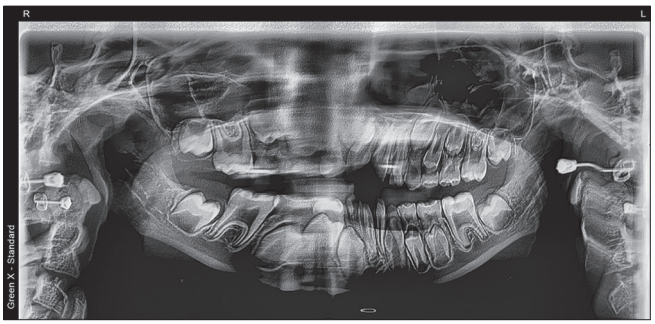

Figure 2: Orthopantomograph of the patient

milestones, facial features, skeletal structure, and skin findings. Moreover, family history helps a lot in the Alazami Syndrome diagnosis. In addition, genetic testing, particularly WES, plays a pivotal role in confirming the diagnosis of Alazami Syndrome and identifying the specific *LARP7* mutations involved.[2,5,7-9,11] Regarding the dental perspective, it can be concluded that the modality of treatment is better to be chosen according to the patient's needs and his family preferences. The periodic examination, regular follow-up, and the concept of anticipatory guidance should be followed along with the multi-disciplinary approach with other medical/dental specialties to address such patients' needs.[14] Dental patients with such rare disorders are struggling to get access to specialized dental care.[15] The lessons should be learned from such cases that the time and efforts should be dedicated to the diagnosis, preparation for treatment, execution of therapeutic interventions, and follow-up. However, further research is needed to delineate the full spectrum of clinical manifestations and their frequency of the Alazami Syndrome. Moreover, to establish clearer

genotype-phenotype correlations, connect specific *LARP7* mutations to features of Alazami Syndrome. In addition, investigating the underlying cellular and molecular mechanisms of Alazami Syndrome paves the way for the development of potential therapies. By combining clinical expertise with advanced genetic technologies, researchers and clinicians can improve the diagnosis and management of Alazami Syndrome, offering better care and support for individuals and families affected by this rare disorder.

The patient's family was having concerns regarding treatment under general anesthesia safety for their kid. Their concerns were addressed with active listening and effective communication during the whole treatment journey. In the end, they expressed their happiness and satisfaction with the result of the dental treatment.

Conclusion

It can be concluded that the patient's behavioral and intellectual challenges affect the diagnosis. Treatment should be tailored to meet the patient's and family's needs. Regular follow-ups and a multi-disciplinary approach are essential for care. Access to specialized dental care is limited for patients with rare disorders. Emphasizing thorough diagnosis, treatment preparation, and follow-up is vital. More research is needed to fully understand the syndrome.

Patient's Family Perspective

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Informed Consent

Informed consent to publish this report was taken from the patient's father.

Data Availability Statement

Not applicable.

Conflict of Interest

The authors have no conflict of interest to declare.

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