Alazami syndrome in a Saudi girl: a case report

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Abstract

The assembly of profound global developmental and intellectual delay, short stature and severe growth restriction, certain characteristic dysmorphic facial features, with the occasional inclusion of behavioral abnormalities, sensory disturbances, as well as some vague bony involvement that can be rather inconsistent, all constitute an extraordinarily uncommon clinical entity coined as “Alazami Syndrome”, the diagnosis of which can be further established by genetic studies confirming the autosomal recessive biallelic frameshift mutations in the LARP7 gene, culminating in a complex and novel form of primordial dwarfism (PD). Herein, we report a patient presenting with this disease, comorbid with pathogenetic variants in SEPSECS mRNA as well, which cause an amalgamation of central nervous system anomalies that include microcephaly, atrophy, mental retardation, and epilepsy, termed as “Pontocerebellar hypoplasia”, accentuating the rarity of our case, as no such variants of these ailments have been formerly defined in preexisting literature. Genetic sequencing of our patient provides further affirmation of the culpability of the pathogenetic variants for each respective condition, and which suggests a potential connection between Alazami syndrome and other genetic malformation disorders.

Keywords: Alazami, syndrome, Saudi, girl, case, report

Introduction

Alazami syndrome (AS) is an autosomal recessive disorder caused by homozygous or compound heterozygous mutations in La ribonucleo protein 7, a transcriptional regulator (LARP7). This gene encodes a protein found in the 7SK snRNP (small nuclear ribonucleoprotein) (1). SnRNP complex inhibits the positive transcription elongation factor b, cyclin-dependent kinase, required for arrested RNA polymerase II to initiate transcription elongation at the promoter, a pseudogene for this gene is located on chromosome 3; alternative splicing gives rise to multiple transcript variants (2). It is a Syndromic form of primitive dwarfism, characterized by short stature and severe growth restriction. Patients with Alazami syndrome present with severe intellectual disability and characteristic facial features such as zygomatic hypoplasia, deep eyes, wide nose, short philtrum, and macrostomia (3). There are some nonspecific skeletal findings that are inconsistent such as scoliosis and mild epiphyseal changes of the proximal phalanx. Such cases are extremely rare. Fewer than 30 cases have been reported worldwide (4). Laboratory investigations would reveal normal plasma amino acids and acylcarnitines, urinary organic acids, very long chain fatty acids, CBC, kidney profile, and bone profile. MRI performed on 2 patients diagnosed with AS showed unilateral mild insular and anterior cortical thickening of the prefrontal gyrus, the other was unremarkable (5).

The diagnosis of Alazami syndrome is confirmed by Whole-exome sequencing (WES) which will identify a homozygous pathogenic variant in exon 12 of LARP 7. Management is multidisciplinary and based on clinical manifestations, with lifelong follow-up. Most people require varying degrees of assistance with daily activities. Neuropsychiatric support, speech therapy, and educational support are effective. Life expectancy is currently unknown. Affected individuals have been reported to reach early adulthood and the degree of autonomy depends on the severity of intellectual disability and language delay.

Case presentation

We present a ten-year-old female patient with a primary complaint of global retardation, development delay, cognitive deficit, and localization-related partial idiopathic epilepsy and epileptic syndromes with localized onset seizures. There was a positive family history of consanguinity and a similar condition; the patient's sibling was diagnosed with global retardation. The patient was on oral levetiracetam (Keppra), an anticonvulsant, oral topiramate (Ipramax), a carbonic anhydrase inhibitor, 25 milligrams taken twice daily for three months, and oral atomoxetine (Strattera) a selective norepinephrine (noradrenaline) reuptake inhibitor. On examination, her height and weight were below the 3rd percentile; she weighed 13 kilograms, and her height was 107 centimeters. An awake digital electroencephalogram (EEG) record showed some multifocal epileptiform discharges superimposed on diffuse background slowing. The beta wave showed 15-20 hertz (Hz), low voltage, and diffuse. The theta wave showed 4-5 Hz, low-medium voltage, irregular, and intermixed diffusely, and the delta wave showed 2 Hz, medium voltage, irregular, and diffuse. There was evidence of multifocal spikes involving C4 and F3 independently, and no driving response was noted.

Eight months later, the patient's condition was under control, and we ordered Whole-exome sequencing, which led to the diagnosis of a rare form of primordial dwarfism, Alazami syndrome. The WES identified SEPSECS, a homozygous silent variant, and homozygous big deletion in LARP7 gene. The Sep (O-Phosphoserine) TRNA: Sec (Selenocysteine) TRNA Synthase SEPSECS (NM_016955.4):c.477A>G(p.Arg159=), Chr4(GRCh37): g.25157729T>C. This sequence change affects codon 195 of the SEPSECS mRNA, but does not change the encoded amino acid sequence. Pathogenic variants in SEPSECS cause pontocerebellar hypoplasia type 2, which is characterized by microcephaly, postnatal onset progressive atrophy of the cerebrum and cerebellum, profound mental retardation, and variable seizures, all of which are evident in our patient. The LARP7 (NM_016648.4):c.507_553-12del (p.Val171fs), Chr4 (GRCh37): g.113568066_113568178del; this sequence change is a deletion of 113 nucleotides that result in removing many amino acids on the LARP7 protein. This alteration is predicted to lead to truncated significantly altered or absent protein.

Discussion

Alazami syndrome (AS) is a rare form of primordial dwarfism (PD). In a paper published in 2012, Alazami et al describe a consanguineous family in Saudi Arabia in which three interrelated branches have a total of 10 children with PD, dysmorphic features, and inconsistent skeletal findings. Further investigations revealed a frameshift mutation in LARP7 which causes a novel form of PD. This autosomal recessive disease is characterized by marked global developmental delay, short stature, varying intellectual retardation, and distinct dysmorphic facial features including, triangular face, scant eyebrows, deeply set eyes, malar hypoplasia, wide nose, short philtrum, and macrostomia (6). It can also present with behavioral abnormalities such as anxiety and hypersensitivity to tactile and auditory stimuli (7). This syndrome is caused by biallelic mutations of LARP7 gene, found on chromosome 4q25, which causes 7SK snRNP depletion (8). 7SK plays a role in the expression of several genes by inhibiting positive transcription elongation factor b (P-TEFb) and competing with DNA for binding to HMGA1, thus directly controlling its activity (9).

Pontocerebellar hypoplasia (PCH) is a group of heterogenous neurodegenerative disorders with a predominantly antenatal onset. PCH was first reported in 1917, but its clinical characteristics were primarily described by Krause in 1928. It is classified into 11 types based on distinctive clinical elements and genetic mutations. Patients with PCH have severe atrophy or hypoplasia of the pons and cerebellum. However, motor and cognitive impairments as well as the involvement

of supratentorial structures are inconsistent. PCH2D is attributable to mutations in the SEPSECS gene and encompasses a spectrum of clinical severity. Patients with normal motor development initially and cognitive disability with motor decline and pediatric onset ataxia have been reported. Additionally, some patients completely lack pontine hypoplasia (10). Our patient presented with dwarfism, developmental retardation, cognitive disability, and idiopathic epileptic seizures of localized onset, fulfilling some aspects of both AS and PCH2D.

The results of Whole-exome sequencing (WES) reveal two distinct genetic mutations, specifically a frameshifting LARP7 mutation and a synonymous SEPSECS mutation. It is unclear if the concurrence of the identified variants in LARP7 and SEPSECS play a part in the disease of the patient. Further investigations are warranted to demonstrate their clinical significance. Analogous to our patient, a case report by Patalan et al depicts a patient that was diagnosed with Phenylketonuria in addition to AS, both of which are caused by genetic mutations (11,12). This suggests a possible association between AS and other genetic abnormalities and requires deeper examination by future research.

Conclusions

In this article, we discussed the phenotype and molecular pathology of Alazami syndrome, and presented a clinical case for reference and example, who was particularly unique by sharing a second genetic affliction, Pontocerebellar hypoplasia. Albeit scarce, the former should still be an important consideration for patients with potential primordial dwarfism, while the latter should be so for patients with intense neurological, developmental, or intellectual deficiencies. Despite considering the complexity of presentation and thus potential management options of Alazami syndrome, it is too rare and understudied to establish any form of sure prognosis. Yet, we hope that shedding more light upon it, alongside our researcher colleagues, would help facilitate a better understanding of the disease, leading to more effective measures of treatment and prevention.

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Authors' contribution

Fawzia Alsharif, Hussein O. Taher, Mohammed Ashoor, Sara A. Alkhamis , Zainab E. Alobaidi, Hossam Alawady, Ahmad W. Alyafi, Refan H. Alshareef , Israa A. Peeran, Hisham Almuzaini, Abdullah Alharthy: all shared in designing the study, they wrote the protocol and planed the study. All collected the data and wrote the case report. All Co-Authors have read and approved the paper. All authors have read and agreed to the published version of the manuscript.

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