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CASE REPORT

Coexistence of junctional epidermolysis bullosa, autosomal recessive deafness type 57, and Angelman syndrome: A case report

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Key Clinical Message: The presence of more than one genetic/genomic disorder is not uncommon. It is therefore essential to continuously consider new signs and symptoms over time. Administration of gene therapy could be extremely difficult in particular situations.

Abstract: A 9-month-old boy presented to our department for evaluation of developmental delay. We found that he was affected by intermediate junctional epidermolysis bullosa (COL17A1, c.3766 + 1G > A, homozygous), Angelman syndrome (5,5 Mb deletion of 15q11.2-q13.1), and autosomal recessive deafness type 57 (PDZD7, c.883C > T, homozygous).

1 | INTRODUCTION

Angelman syndrome (AS, OMIM#105830) is a well-known neurogenetic disorder characterized by the loss of the ubiquitin-protein ligase E3A (*UBEA*) enzyme, which results from an abnormal methylation of the maternally inherited 15q11.2–13.1 region or a pathogenic variant in the maternally derived *UBE3A* gene.[1] The incidence of AS is estimated at 1 in 12,000–20,000 live births.[2]

On the other hand, epidermolysis bullosa (EB) is a rare genetic bullous disorder characterized by skin blistering as a result of mild mechanical trauma. According to the consensus reclassification of inherited EB, it is divided into four broad categories considering the level of skin cleavage: (a) EB simplex, characterized by intraepidermal blistering; (b) junctional EB (JEB, OMIM#619787), characterized by tissue separation within the dermal-epidermal basement membrane; (c) dystrophic EB, characterized by sub-lamina densa blister formation within the upper papillary dermis; and (d) Kindler EB, characterized by the coexistence of multiple levels of tissue separation.[3,4] The overall incidence of EB is estimated at 19.57 per 1 million live births.[5]

In contrast, deafness, the most common sensory disorder, is phenotypically and genetically heterogeneous, with over 113 genes associated with it.[6] Among these, non-syndromic hearing loss is the most common (70%). *PDZD7* is a rare cause of non-syndromic hearing loss, affecting fewer than 20 families.[7]

In this study, we report a case of AS with a coexisting intermediate JEB due to a *COL17A1* gene variant and deafness, autosomal recessive 57 due to *PDZD7* variants, and we discuss the differences in the usual management of both disorders due to their coexistence.

2 | CLINICAL REPORT

Pregnancy was uneventful and he was delivered by C-section indicated for non-reassuring fetal status at 39 gestational weeks with a birth weight of 3970 g (95th percentile). He was born with vesicles, blisters, erosions, and scabs (Figure 1). They were distributed evenly across all the body surfaces and manifested themselves with little or no trauma. EB was suspected at birth, and immunofluorescence antigen mapping and molecular genetic analyses revealed a subepidermal vesicle with an antibody directed against laminin 332, which showed reduced staining in comparison to the control. Antibodies against alpha6 integrin and beta4 integrin stain the epidermal portion (roof) of the subepidermal vesicle, while antibodies against laminin 333, collagen IV, and collagen VII stain the dermal portion of the vesicle. These results are consistent with junctional EB.[3] Moreover, the clinical exome reported the homozygous *COL17A1* (NM_000494.4):c.3766 + 1G > A variant, reported as pathogenic by the ACMG criteria and ClinVar (RCV001352740), confirming the diagnosis of junctional EB. Both parents were carriers of the variant (Figure 2). In the family history, it is important to note the consanguinity of parents (Spanish Rome-ethnicity) and other affected relatives with both deafness and EB. It was impossible to obtain a reliable family tree due to the large size of the family and it is crucial to highlight that the family history of deafness was not collected on the initial appointment, but rather over the course of the history.

As early as 2 months of age, failure to thrive was observed. At the age of 8 months, he was hospitalized due to respiratory failure caused by laryngotracheomalacia and croup. At the age of 9 months he has been seen by the Pediatric Neurological department due to global
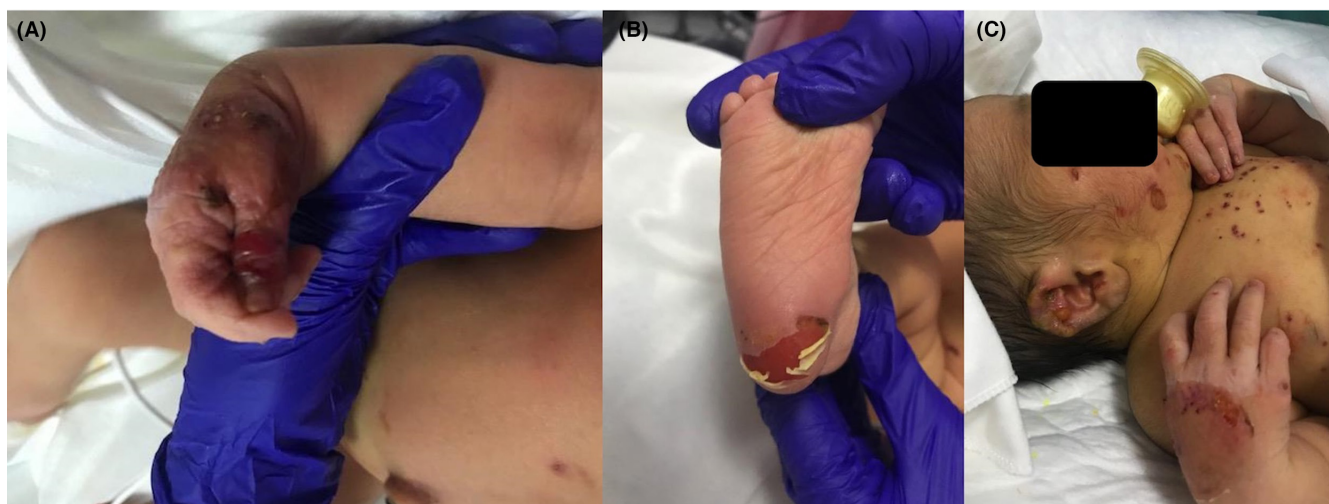

FIGURE 1 Neonatal intermediate junctional EB with (A) ulceration and crusting in the right hand, (B) right heel, and (C) widespread skin blistering. The contents of the blisters are either clear or serohemorrhagic, and they are found in areas of high friction.

FIGURE 2 Sanger sequencing demonstrates (A) the segregation of the *COL17A1* (NM_000494.4):c.3766 + 1G > A and (B) the segregation of the *PDZD7* (NM_001195263.2):c.883C > T/p. Pro295Ser variant.
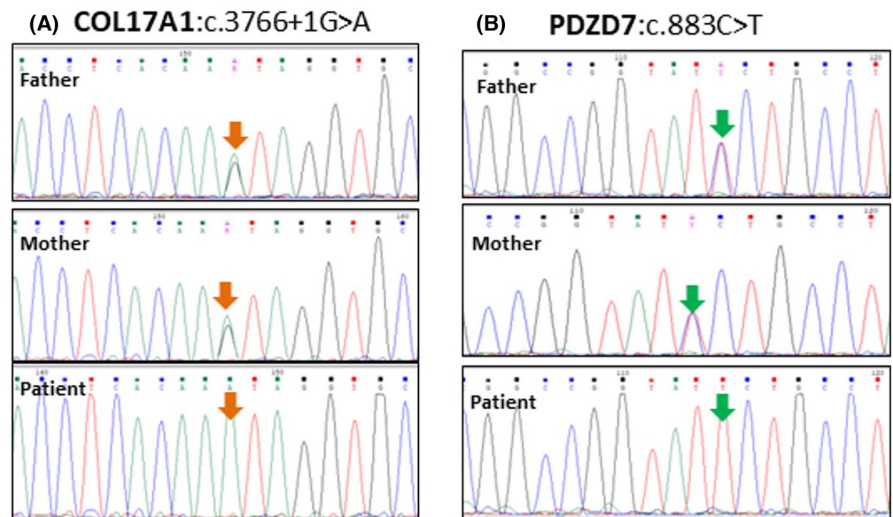
developmental delay. During the follow-up period, dysmorphisms including facial hypotonia, low-set ears, and micrognathia became more apparent, as did the persistence of the feeding disorder and global developmental delay. He achieved unstable head support at the age of 8 months and was unable to stay autonomously seated at the age of 9 months. At 12 months, auditory-evoked potentials demonstrated moderate–severe bilateral hipoacusia. At 17 months of age, he was found to have global hypotonia with predominantly axial, stable head support and instability when seated, with a preference for the supine position. He had appropriate eye contact and followed up objects easily. He was very sociable; he smiled and engaged in play. Despite the fact that his use of hands was suboptimal for his age, he picked up objects, moved them erratically, brought them to his mouth, or threw them to the ground. He babbled but had not said a word. No abnormal movements or seizures had been perceived by the family. At the age of 1 year and 5 months, he weighed 9,8 kg (7th percentile, −1,48 SD), measured 81.5 cm in length (42nd percentile, −0.21 SD), and had a cranial circumference of 43.5 cm (<1st percentile, −3.7 SD).

Considering the occurrence of global developmental delay and moderate–severe bilateral hipoacusia that were observable at this age but not in the newborn period, a re-analysis of exome sequencing data detected a 5,5 Mb deletion in the Prader Willi-Angelman region (15q11.2-q13.1, chr15:23006153-28566627x1) that was subsequently confirmed in the maternal allele by MLPA, with the typical AS methylation pattern. Both parents were examined, but neither exhibited this pathological pattern. In addition, deafness-related genes were analyzed in light of the deafness-affected kinship. A homozygous variant in the *PDZD7* gene (NM_001195263.2):c.883C > T/p.Pro295Ser was found. This variant was inherited from both the father and the mother (Figure 2). According to ACMG guidelines, this variant is classified as a variant of unknown significance (VOUS, PM2, PP1, BP1). This variant was not found in gnomAD genomes or exomes. Moreover, there was a cosegregation with phenotype in multiple affected family members. The Mutation Taster and SIFT prediction are uncertain; however, the PROVEAN prediction is pathogenic. This variant has a Combined Annotation Dependent Depletion (CADD) of 26.

The legal guardians gave their written consent for publication, and the study received ethical approval by the Ethics Committee (ART-06-22).

3 | DISCUSSION

We described the first case of AS and intermediate JEB co-existence. As a newborn, the patient was suspected of having JEB due to the presence of the characteristic skin lesion associated with mild trauma, which was confirmed by the finding of pathogenic variants of the *COL17A1* gene in the exome. However, additional signs and symptoms (global developmental delay, hypotonia, hearing impairment, feeding difficulties, failure to thrive, and consanguineous family history) prompted us to continue investigating additional genetic disorders. As a result of the exome reanalysis, a 15q11-q13 deletion was found. Subsequent studies established that this deletion was inherited from the maternal allele, confirming the AS diagnosis. It is critical to emphasize how essential it is to continuously consider new signs and symptoms over time, as this may result in a more accurate or even a new diagnosis. In this case, the JEB diagnosis did not adequately explain the neurological symptoms. Taking the incidence of both disorders into account, the combined occurrences of both events would be approximately 0.97 cases per billion births.

JEB can have polymorphic phenotypes and vary in severity. The severe form is a more serious form characterized by blisters present at birth or during the neonatal

period. Because of feeding difficulties, breathing difficulties, life-threatening infections, and deteriorating nutritional status, these patients typically do not survive beyond the first year of life.[3] The intermediate form is a milder form that affects predominantly the hands, feet, knees, and elbows. It typically improves after the newborn period and is associated with a normal lifespan, including alopecia and onychodystrophy, as well as dental enamel pitting. Breathing problems and other serious complications are uncommon. JEB has been linked to a number of genes, including *LAMB3*, *LAMA3*, *LAMC2*, *ITGA3*, *ITGA6*, *ITGB4*, and *COL17A1*. Our patient presents an intermediate JEB due to homozygous *COL17A1* variants.

PDZD7 is a scaffolding protein that is highly expressed in the stereocilia of inner ear hair cells and in the connecting cilia of photoreceptors. Booth et al.[6] reported the first association of autosomal recessive non-syndromic hearing loss (OMIM#618003) resulting from *PDZD7* variants. Often, the onset occurs during early childhood and, in some cases, during the prelingual stage. In these patients, hearing loss ranges from moderate-to-severe and may even be progressive.[7] In addition to AS, *PDZD7*-deafness may provide a significant barrier to his language development. Currently, he is a noncommunicative infant; he does not cry, babble, or demand his parents.

Around 80–90% of patients with AS develop epilepsy. The onset of epilepsy is most common between the ages of one and three. However, approximately 25% of patients develop epilepsy before the age of one. The deletion subtype is most frequently associated with severe epilepsy, followed by patients with the *UBE3A* mutation.[8] In general, non-deletion patients may experience seizures with a relatively late onset. Patients with AS may exhibit a variety of distinct EEG abnormalities, either alone or in combination, conforming to the typical pattern that normally changes with age.[2] There is no difference in EEG findings in AS patients with or without epileptic seizures.[9] Frequently, the typical EEG is more abnormal than the clinical appearance suggests, and it may suggest seizures when none exist. Children with AS are at risk of medication overuse due to the possibility that their movement abnormalities or attention deficits are misinterpreted as seizures and because EEG abnormalities can persist even when seizures are controlled.[10]

EEG abnormalities have been proposed as a reliable biomarker for AS in research studies. However, EEG features must be rigorously evaluated before they can be used in clinical trials as an objectively quantifiable measure with confidence. Taking this into consideration, we have decided to delay performing a videoEEG until clear clinical seizures or behavioral problems are present, since the procedure may lead to new skin lesions. In general terms, due to the stability of the patient and the special vulnerability of his skin, all physical procedures have been limited by the clinical team.

Remarkably, AS is characterized by hypermotoric behavior that occasionally results in auto-aggressive lesions. This situation can be exacerbated in this patient, where skin lesions occur as a result of minor trauma. In addition to neuroleptic treatment to help improve behavior, there have been tremendous advances in genetic therapy for AS patients in recent years.

On the one hand, therapies that try to unsilence the parental allele are increasing and are being evaluated in clinical trials, mainly antisense oligonucleotides (AOS) that, unfortunately, need to be administered by lumbar tap (Neurotherapeutics and Roche, clinical trials NCT04106557 and NCT04428281, respectively). In preclinical studies, Topotecan, an antisense oligonucleotide therapy, demonstrated both in vitro and in vivo efficacy. In vitro, it resulted in the restoration of functional Ube3a to wild-type levels in cultures of primary cortical neurons from mice deficient in maternal Ube3a due to a null mutation. Topotecan increases paternal Ube3a expression primarily in spinal cord neurons when administered intrathecally, and the effects last for 12 weeks after the last dose. Because topotecan has a low bioavailability in the CNS, other topoisomerase I inhibitors were investigated, and indotecan was found to have a better pharmacological profile.[11] Finally, some CRISPR-Cas9-guided interventions also try to unsilence the parental *UBE3A* gene. However, in the context of our patient, all therapies administered via lumbar tap may be hazardous due to the procedure itself and may be contrary to best interest of the patient. On the other hand, patients with AS can benefit from gene therapy (both ex vivo and in vivo approaches are under development).

In summary, ongoing evaluation of patient signs and symptoms enables reanalysis of exome data sequencing, the diagnosis of coexisting diseases, and can facilitate access to new treatments. The adaptation of evidence-based-recommendations in the follow up of complex patients is essential. Only patient-centered medical assistance and the coordination of the different specialists could guarantee the best quality of life and comfort in these complex situations. Last but not least, while the development of new therapeutic approaches is encouraging, the administration procedure for our patients could be extremely difficult.

AUTHOR CONTRIBUTIONS

Maria Eugenia Amato: Data curation; formal analysis. **Silvia Ricart:** Formal analysis. **Maria Asunción Vicente:** Formal analysis. **Loreto Martorell:** Data curation; formal analysis. **Judith Armstrong:** Data curation; formal analysis. **Guerau Fernandez Insern:**

Data curation; formal analysis. **José Manuel Mascaro:** Data curation; formal analysis. **Sol Balcells:** Data curation; formal analysis. **Itziar Alonso:** Data curation; formal analysis. **Mercedes Serrano:** Data curation; formal analysis. **Juan Dario Ortigoza Escobar:** Conceptualization; data curation; formal analysis; project administration.

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REFERENCES
1. Wang TS, Tsai WH, Tsai LP, Wong SB. Clinical characteristics and epilepsy in genomic imprinting disorders: Angelman syndrome and Prader-Willi syndrome. *Tzu chi Med J*. 2020;32(2):137-144. doi:10.4103/tcmj.tcmj_103_19
2. Debopam S. Epilepsy in Angelman syndrome: a scoping review. *Brain and Development*. 2021;43(1):32-34. doi:10.1016/j.braindev.2020.08.014.Epilepsy
3. Has C, Bauer JW, Bodemer C, et al. Consensus reclassification of inherited epidermolysis bullosa and other disorders with skin fragility. *Br J Dermatol*. 2020;183(4):614-627. doi:10.1111/bjd.18921
4. Vahidnezhad H, Youssefian L, Saeidian AH, et al. Next generation sequencing identifies double homozygous mutations in two distinct genes (EXPH5 and COL17A1) in a patient with concomitant simplex and junctional epidermolysis bullosa. *Hum Mutat*. 2018;39(10):1349-1354. doi:10.1002/humu.23592
5. Fine JD. Epidemiology of inherited epidermolysis bullosa based on incidence and prevalence estimates from the national epidermolysis bullosa registry. *JAMA Dermatol*. 2016;152(11):1231-1238. doi:10.1001/jamadermatol.2016.2473
6. Booth KT, Azaiez H, Kahrizi K, et al. PDZD7 and hearing loss: more than just a modifier. *Am J Med Genet A*. 2015;167A(12):2957-2965. doi:10.1002/ajmg.a.37274.PDZD7
7. Fahimi H, Behroozi S, Noavar S, Parvini F. A novel recessive PDZD7 bi-allelic mutation in an Iranian family with non-syndromic hearing loss. *BMC Med Genet*. 2021;14(1):4-11. doi:10.1186/s12920-021-00884-4
8. Thibert RL, Conant KD, Braun EK, et al. Epilepsy in Angelman syndrome: a questionnaire-based assessment of the natural history and current treatment options. *Epilepsia*. 2009;50(11):2369-2376. doi:10.1111/j.1528-1167.2009.02108.x
9. Laan LAEM, Vein AA. Angelman syndrome: is there a characteristic EEG? *Brain Dev*. 2005;27(2):80-87. doi:10.1016/j.braindev.2003.09.013
10. Williams CA, Peters SU, Calculator SN. Facts about Angelman Syndrome. *Angelman Org*. 2009;34:1-24.
11. Markati T, Duis J, Servais L. Therapies in preclinical and clinical development for Angelman syndrome. *Expert Opin Investig Drugs*. 2021;30(7):709-720. doi:10.1080/13543784.2021.1939674