Case Report of Dual Diagnosis of Chronic Intervillositis and Helsmoortel-Van der Aa Syndrome in an Infant with Intrauterine Growth Restriction and Premature Birth

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Keywords

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Abstract

Chronic intervillositis of unknown etiology (CIUE) is a rare placental pathology associated with intrauterine growth restriction. Helsmoortel-Van der Aa syndrome (HVDAS) is a neurodevelopmental disorder caused by heterozygous mutations in the Activity-Dependent Neuroprotective Protein (*ADNP*) gene.

We describe an extreme preterm infant born due to CIUE, presenting with proportionate microcephaly, facial dysmorphism, failure to thrive, and neurodevelopmental delay. Whole-exome sequencing (WES) identified a pathogenic variant in the *ADNP* gene.

Our findings suggest that the dual diagnosis of CIUE and HVDAS contributed to the proband's clinical presentation. This case highlights the importance of WES in evaluating complex neonatal phenotypes.

Introduction

Chronic intervillositis of unknown etiology (CIUE) is a rare pathology of the placenta affecting 0.2% of pregnancies. It is diagnosed histologically after exclusion of congenital infections, and the identification of maternal CD68+ histiocytes in the intervillous space. CIUE can lead to first-trimester miscarriages, fetal growth restriction (FGR), or late intrauterine fetal death. Its pathophysiology remains unknown (1).

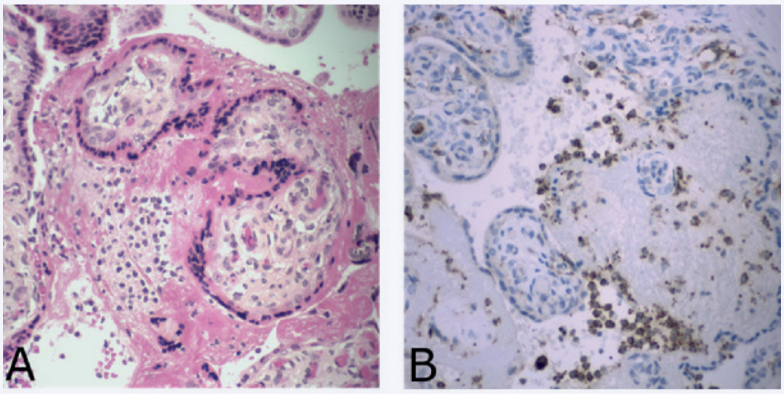
Helsmoortel-Van der Aa syndrome (HVDAS) (MIM: 615873) is a monogenic neurodevelopmental disorder characterized by mild to severe intellectual disability, language and motor delay, dysmorphic features and a variable range of other symptoms (2). Birth weight, length, and head circumference are within the normal range, and extreme prematurity has not been previously described in individuals with HVDAS (3). HVDAS is caused by heterozygous variants in the *ADNP* gene, which encodes a transcription factor of the SWI/SNF (BAF) chromatin remodeling complex, essential for the transition from proliferating neural stem cells to post-mitotic neurons during brain development (4). Most reported variants are de novo heterozygous nonsense variants in the last and largest exon of the gene (3).

Here, we describe an infant diagnosed with both CIUE and HVDAS during the neonatal period, presenting with manifestations consistent with both conditions.

Case Presentation

The proband is the first child born to a healthy, non-consanguineous Caucasian couple. Routine ultrasounds at the first and second trimesters, as well as non-invasive prenatal testing, were normal. Maternal high blood pressure and congenital infection were excluded during and at the end of pregnancy. At 27 weeks and 4 days of gestation, a fetal ultrasound revealed FGR, oligohydramnios, and abnormal uterine artery Doppler flow. A female preterm infant was born at 27 weeks and 5 days via urgent C-section due to severe fetal heart rate deceleration. Pulmonary maturation was not induced before birth. Birth weight was 570 g, and the Apgar scores were 6, 8, and 8 at one, five, and ten minutes, respectively. Stabilization in the delivery room included continuous positive airway pressure (CPAP) and oxygen therapy. A single dose of surfactant and mechanical ventilation were required for hyaline membrane disease. Physical examination revealed weight,

FIGURE 1: a. Hematoxylin and eosin staining shows a histiocyte infiltrate in an intervillous space. Magnification 20x. / b. Positive anti-CD68 immunostaining highlights the histiocyte infiltrate. Magnification 20x.



length, and head circumference at -1.81 SD, -0.63 SD, and -1.99 SD, respectively, according to the Fenton Preterm Growth Chart.

The patient required prolonged CPAP due to bronchopulmonary dysplasia and central sleep apnea. An echocardiogram at 36 weeks of postmenstrual age revealed an isolated large patent ductus arteriosus (PDA), which required surgical ligation. Persistent high blood pressure due to proximal renal tubulopathy was controlled with medical treatment. Severe hypokalemia and hypophosphatemia required long-term supplementation. Enteral nutrition with breast milk was progressively increased and well tolerated, with full feeding autonomy achieved on day 89. Despite fortified breast milk, recurrent episodes of diarrhea and failure to thrive were observed. Clinical evaluation revealed a prominent forehead with a high anterior hairline, small ears with a low insertion, and a short nose. A neurological assessment at term revealed psychomotor and neurodevelopmental delay, with preferential extension of all four limbs and asymmetric dominant right-side movements, and limited visual contact. Standard electroencephalogram, auditory brainstem response, brain magnetic resonance imaging, and ophthalmologic examinations were normal.

The patient was discharged at 44 weeks of postmenstrual age. Her weight, length, and head circumference were -2.20 SD, -1.94 SD, and -1.91 SD, respectively, according to the Fenton Preterm Growth Chart.

Placental histological examination

Placenta histological analysis showed severe CIUE, characterized by scattered and focal perivillous fibrin deposits with a transmural distribution, intervillous infiltration of CD68-positive macrophages, and polymorphonuclear neutrophils, as shown in Figure 1.

Genetic Analysis

An array-comparative genomic hybridization (aCGH) was performed at 27 weeks and 4 days of gestation, which did not reveal any copy number variation. A trio whole exome sequencing (WES) was performed after birth, at 35 weeks and 6 days of postmenstrual age for a suspicious phenotype (dysmorphic facial traits, failure to thrive and neurodevelopmental delay). It revealed a de novo heterozygous c.516C>G variant in exon 5 of the *ADNP* gene (NM_015339.2), leading to a premature stop codon in place of a tyrosine at position 172 of the protein (p.Tyr172*). The result was confirmed by Sanger sequencing. This variant is absent in both the control population (gnomADv4 (broadinstitute.org)) and in the ClinVar9 databases and has not been previously described. Based on its nonsense nature, its close proximity to known pathogenic nonsense variants, and its de novo occurrence, it was classified as a pathogenic variant according to the American College of Medical Genetics and Genomics (ACMG) guidelines. (3,5)

Clinical assessment at 12 months of corrected age

At 12 months of corrected age, the patient exhibited good social contact, enjoying interactions with both adults and other toddlers. However, she was easily startled by her environment and frequently experienced episodes of teeth grinding.

Her weight remained small (6900 g, -2.1 SD), with associated microcephaly (42.5 cm, -2 SD), according to the Fenton Preterm Growth Chart. She was primarily fed artificial milk, with introduction of solid foods. While she no longer experienced persistent diarrhea, she had periods of severe constipation.

Motor development was moderately delayed despite regular physical therapy sessions. She was slightly hypotonic and did not crawl. Although she could not acquire a seated position by herself, she was able to maintain a seated posture. She had not yet started walking but could stand with support. Spontaneous movements were limited. She demonstrated good manipulation of objects with both hands and appropriate distal thumb-index pinch. She could produce sounds and mimic two-syllable words. A Bayley-III Scale evaluation revealed delays of 5, 2, 1, 5, and 7 months in cognition, receptive and expressive language, fine motor skills, and gross motor skills, respectively.

She received daily inhaled fluticasone and on-demand inhaled salbutamol for bronchopulmonary dysplasia. She was regularly monitored for high blood pressure, which had caused secondary left-sided dilated cardiomyopathy, which resolved following adequate treatment.

Methods

The aCGH was performed on a CytoSure Constitutional v3 8×60k array (Oxford Gene Technology). Maternal contamination was excluded by quantitative fluorescent-polymerase chain reaction (Devyser Complete v2).

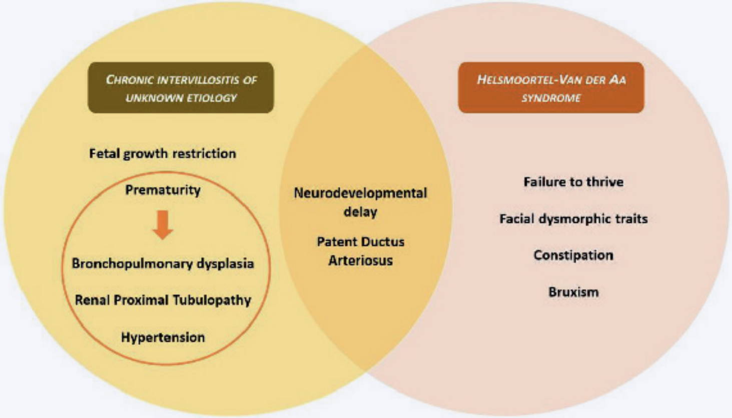
The WES library preparation was performed using the KAPA HyperPrep/HyperPlus Library Preparation Kit (Roche NimbleGen Inc.). In-house SeqCap EZ Choice XL Probes (Roche NimbleGen Inc.) targeting the coding exons of 4,867 genes associated with Mendelian disorders were used for library preparation. Libraries were sequenced on Illumina HiSeq 1500/NovaSeq 6000 (Illumina Inc.). The bioinformatics pipeline was run at Brussels Interuniversity Genomics High Throughput core (BRIGHTcore) (http://www.brightcore.be/). Reads were aligned to the reference genome (GRCh37/hg19) using the Burrows-Wheeler Aligner (version 0.7.10), and variant calling was performed using Genome Analysis Toolkit (version 3.3).

Written informed consent was obtained from both parents for all genetic investigations, including aCGH and WES. The family received appropriate genetic counseling before and after testing, and consented to the use of de-identified clinical data for research and educational purposes.

Discussion

The pathophysiology of CIUE remains incompletely elucidated, though it appears to involve maternal pathological processes characterized by maternal-derived lesions within the intervillous spaces. Studies of discordant dizygotic twins suggest a maternal alloimmune response against fetoplacental histocompatibility antigens as the underlying mechanism (6). This placental pathology leads to adverse perinatal outcomes, including fetal loss after 22 weeks' gestation, FGR due to placental insufficiency, and preterm delivery, with high recurrence rates in subsequent pregnancies (1,6). In our patient, we hypothesize that the severe FGR and extreme prematurity at 27 weeks resulted directly from the placental pathology associated with CIUE.

FIGURE 2: Clinical findings in concurrent CIUE and HVDAS. *Yellow*: complications attributable to placental pathology and prematurity; *Orange*: features consistent with reported HVDAS phenotype; *Overlap*: findings potentially influenced by multiple factors including genetic syndrome and prematurity.



However, the constellation of dysmorphic facial features and persistent failure to thrive could not be explained by CIUE-related prematurity alone. These findings, combined with neurodevelopmental delays that appeared disproportionate to the degree of prematurity, prompted comprehensive genetic evaluation. WES revealed a de novo pathogenic variant in *ADNP*, confirming a diagnosis of HVDAS. Notably, extreme prematurity is not a typical feature of HVDAS—in a cohort of 78 individuals, gestational age ranged from 30 to 42 weeks (3). Only one previous case reported delivery at 35 weeks due to symmetrical FGR, though this occurred with normal uterine artery Doppler studies, contrasting with our patient's abnormal findings (7).

The dual diagnosis created a complex clinical picture requiring careful phenotypic attribution. HVDAS-specific features became apparent over time and included dysmorphic facial characteristics, feeding difficulties leading to failure to thrive (reported in 83% of HVDAS patients), bruxism, and chronic constipation—none typically associated with prematurity alone (2,3). Conversely, some manifestations such as neurodevelopmental delay and patent ductus arteriosus likely reflected combined effects of extreme prematurity and the underlying genetic syndrome. Whether HVDAS contributed to the FGR remains unclear, as FGR is not a feature consistently reported in this syndrome (3).

This case exemplifies the clinical utility of early genetic testing recommended by ACMG guidelines for managing patients with congenital anomalies during the first year of life (8). The HVDAS diagnosis enabled targeted interventions—intensive physical therapy was initiated to address motor delays, while the recognition of syndrome-specific features (bruxism, constipation) eliminated the need for extensive additional investigations. Early genetic diagnosis also facilitated appropriate family counseling and informed medical management decisions, demonstrating how genetic testing can reduce diagnostic uncertainty in complex neonatal phenotypes (9).

The genetic findings have important implications for future reproductive planning. De novo variants carry a low recurrence risk (1-2%) due to potential parental germline mosaicism, making prenatal diagnosis generally unnecessary, though personalized risk assessment through parental germline sequencing can be offered (10). In contrast, CIUE demonstrates a significantly higher recurrence rate (23% pregnancy loss), requiring intensive prenatal surveillance in future pregnancies. Current treatment approaches with immunomodulatory therapy (corticosteroids, hydroxychloroquine) may reduce lesion severity, though outcomes remain limited (1). This dual risk profile necessitates comprehensive reproductive counseling addressing both conditions.

Conclusion

Our case underscores the clinical utility of WES in the perinatal period for elucidating complex phenotypes that cannot be explained by placental histopathology alone. Early genetic diagnosis facilitated a comprehensive, multidisciplinary approach to care and provided the family with timely reproductive counseling. To our knowledge, this is only the second reported case of HVDAS with symmetrical FGR and a perinatal presentation, which raises the possibility that FGR could represent a rare manifestation within the broader phenotypic spectrum of the disorder. Further reports will be necessary to clarify whether this association is incidental or clinically meaningful.

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