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HDAC8 - Related Cornelia de Lange Syndrome (CdLS5): An Atypical Neonatal Presentation

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Abstract: ***Cornelia de Lange syndrome (CdLS) is a genetically heterogeneous cohesinopathy caused by variants in NIPBL, SMC1A, SMC3, RAD21, or HDAC8, with the HDAC8-related subtype (CdLS5) accounting for a small minority of cases and following X-linked dominant inheritance. We report a late-preterm, low-birth-weight female neonate who presented with a difficult perinatal transition, culture-negative sepsis, hypernatremia, neonatal seizures, hyperbilirubinemia, microcephaly, and ambiguous genitalia, initially raising suspicion of congenital adrenal hyperplasia (CAH). Endocrine work-up (testosterone, cortisol, DHEA-S, 17-hydroxyprogesterone and plasma renin activity) did not support classic CAH. Cranial MRI at follow-up showed a simplified gyral pattern with underopercularised sylvian fissures and prominent trigones, suggestive of a primary microcephaly syndrome. Whole exome sequencing subsequently identified a heterozygous nonsense variant in HDAC8 (NM_018486.3:c.490C>T, p.Arg164Ter), classified as pathogenic and previously reported in association with Cornelia de Lange syndrome 5, establishing the diagnosis. This case highlights the importance of considering cohesinopathies in the differential diagnosis of a neonate with primary microcephaly and atypical genitalia once classic CAH has been excluded, and demonstrates the diagnostic yield of exome sequencing in phenotypically atypical presentations of CdLS.***

Keywords: Cornelia de Lange syndrome, HDAC8, cohesinopathy, primary microcephaly, ambiguous genitalia, neonatal seizures, whole exome sequencing

1. Introduction

Cornelia de Lange syndrome (CdLS) is an archetypal cohesinopathy characterized by distinctive craniofacial dysmorphism, pre- and postnatal growth restriction, limb anomalies, and intellectual disability, with an estimated prevalence of 1 in 10,000–30,000 live births.[1] Pathogenic variants in *NIPBL* account for approximately 60% of cases (CdLS1), while variants in the core cohesin components *SMC1A*, *SMC3*, and *RAD21*, and the cohesin-deacetylase *HDAC8*, together account for most of the remainder[1, 2]. *HDAC8*-related CdLS (CdLS5, OMIM #300882) follows X-linked dominant inheritance and tends to produce a milder or atypical craniofacial phenotype than classic NIPBL-related disease, which can delay clinical recognition, particularly in the neonatal period when overlapping features such as microcephaly and genital anomalies may instead prompt an endocrine work-up for disorders of sex development or congenital adrenal hyperplasia (CAH)[1, 3]. We describe a neonate in whom a complicated perinatal course and suspected CAH were the initial presenting concerns, with the eventual diagnosis of CdLS5 established only on exome sequencing performed for syndromic primary microcephaly.

2. Case Report

A female neonate was born at 37 weeks of gestation by emergency lower-segment caesarean section, indicated for pregnancy-induced hypertension with fetal bradycardia, to a mother in her second gravida (G2A1) pregnancy conceived spontaneously. The pregnancy was complicated by pregnancy-induced hypertension, gestational diabetes mellitus, and maternal hypothyroidism. The parents were non-consanguineous. The baby was born with a birth weight of 1.7 kg and required resuscitation, intubation, and mechanical ventilation at birth, followed by gradual respiratory weaning to CPAP, low-flow oxygen, and room air.

On DOL 4, the baby developed seizure-like activity and received intravenous levetiracetam. Empirical antibiotics and inotropic support were initiated, and the baby was transferred to our neonatal unit on DOL 6.

On admission, the baby was hemodynamically stable with SpO_2 98% on oxygen support. Neurological examination was unremarkable, with normal tone, activity, cry, and neonatal reflexes. Head circumference was 29.5 cm. Initial blood gas was normal. Sepsis evaluation showed elevated TLC (24,030 cells/mm³) with CRP 2.5 mg/L; blood culture remained sterile, and antibiotics were completed for 7 days as culture-negative sepsis. Transient hypernatremia (Na 156 mmol/L) was corrected with fluid adjustment. Mildly prolonged coagulation parameters were noted, while serum calcium and creatinine were normal.

In view of the difficult perinatal transition, hypoglycemic episodes, and neonatal seizures, pediatric neurology opinion

was sought; electroencephalography was normal and a neurosonogram showed small bilateral grade 1 germinal matrix hemorrhage. Because the external genitalia were atypical in association with microcephaly and a hypoglycemic episode, an endocrine work-up for congenital adrenal hyperplasia and disorders of sex development was initiated. Abdominal ultrasound was normal; pelvic ultrasound showed a normal uterus with non-visualization of both ovaries, for which repeat imaging on follow-up was advised. Hormonal work-up showed testosterone 1.12 ng/mL (reference 0.12–0.21), cortisol 30.4 mg/dL (reference 2.47–11.9), DHEA-S 310.3 mg/dL (reference 108–607), 17-hydroxyprogesterone 2.44 ng/mL (reference 0–8), and plasma renin activity 55 ng/mL/hr (reference 2–35)- a pattern not typical of classic 21-hydroxylase-deficient CAH. Karyotype was normal (46, XX); FISH for Y-chromosome material and a steroid hormone panel were sent for confirmation. TORCH serology was reactive for rubella IgG only, consistent with past maternal/passive immunity. The baby achieved full enteral (paladai) feeds, remained hemodynamically stable in room air, and was discharged on DOL 12 with advice for endocrinology, neurology, and genetics follow-up, including a repeat MRI brain.

3. Follow-up Imaging and Genetic Evaluation

At follow-up in early infancy the baby continued to have feeding intolerance, intermittent fever, cough and cold, and persistent microcephaly, with a head circumference of 35.5 cm at approximately 2 months of age. Examination at that visit additionally noted sparse hair, a stubby nose. MRI of the brain showed a mildly simplified gyral pattern, most pronounced along the frontal lobes, under opercularised sylvian fissures, and mild prominence of the trigones, without features of an acquired insult; vascular flow voids were intact. The overall imaging impression favoured a genetic/primary microcephaly-related disorder, likely of autosomal recessive MCPH-spectrum type on imaging pattern alone. In view of failure to thrive, feeding intolerance, microcephaly, and the described dysmorphic features, clinical exome/whole exome sequencing

(WES) was performed at 9 months of age on a peripheral blood sample (mean on-target sequencing depth 108.33×; 20× coverage 99.32% of target bases).

WES identified a heterozygous nonsense variant in exon 5 of *HDAC8* (NM_018486.3:c.490C>T; chrX: g.72495216G>A; p.Arg164Ter; ENST00000373573.9; read depth 119×), predicted to result in premature truncation of the protein. This variant has previously been reported in patients with Cornelia de Lange syndrome, is absent from population databases (1000 Genomes, gnomAD v2.1/v3.1, TOPMed) and an internal Indian reference dataset, and affects a codon that is conserved across species. Applying ACMG/AMP criteria (PVS1_VeryStrong, PM2_Moderate, PP1_Supporting),[4] the variant was classified as pathogenic, consistent with a diagnosis of Cornelia de Lange syndrome 5 (OMIM #300882), caused by mutations in *HDAC8* (OMIM *300269). No pathogenic copy number variant was detected. Parental segregation studies and formal genetic counselling were recommended to confirm the mode of inheritance and to guide recurrence-risk counselling, since *HDAC8*-related CdLS follows X-linked dominant inheritance and can arise de novo or, less commonly, from a mosaic parent.

Table 1: Summary of the causative molecular finding

Parameter	Finding
Gene (Transcript)	*HDAC8* (NM_018486.3, ENST00000373573.9)
Location	Exon 5
Variant	c.490C>T, p.Arg164Ter
Zygosity	Heterozygous
Associated disease (OMIM)	Cornelia de Lange syndrome 5 (#300882)
Inheritance	X-linked dominant
ACMG classification	Pathogenic (PVS1_VS, PM2_M, PP1_Sup)

4. Discussion

This neonate illustrates two teaching points relevant to neonatal and PICU practice. First, primary microcephaly with atypical genitalia in a neonate is not synonymous with classic CAH, and a hormonal profile inconsistent with 21-hydroxylase deficiency (as here, with a non-suppressed cortisol and only mildly elevated renin) should prompt reconsideration of a syndromic diagnosis rather than repeated CAH-directed work-up alone. Second, cohesinopathies such as CdLS should remain in the differential of syndromic primary microcephaly even when the classical CdLS facial gestalt (synophrys, long philtrum, thin lips, arched eyebrows) is not emphasised in the neonatal record, since *HDAC8*-related disease is recognised to produce a milder or non-classic phenotype than NIPBL-related CdLS.[1, 3, 10]

HDAC8 encodes the histone deacetylase that removes the acetyl mark from SMC3, a core cohesin subunit, and is required for cohesin recycling during the cell cycle.[2, 6] Loss-of-function and missense variants in *HDAC8* impair this deacetylation step and account for roughly 4–5% of molecularly confirmed CdLS.[2, 5] Structural studies have shown that CdLS-associated *HDAC8* missense variants distort the enzyme's substrate-binding channel or catalytic pocket, while truncating variants such as the p.Arg164Ter change identified in this infant are predicted to abolish enzyme function altogether

through loss of the catalytic domain.[6, 7] Because *HDAC8* is X-linked, affected females are typically heterozygous, as in this case, and phenotypic severity can be modified by the pattern of X-inactivation; affected males, when reported, tend to have a more severe phenotype.[1, 3]

The perinatal course in this infant- difficult transition at birth, culture-negative sepsis, hypernatremia, and neonatal seizures- is not specific to CdLS and was managed along conventional neonatal intensive care lines (empirical antibiotics, fluid and electrolyte correction, and levetiracetam for seizures), consistent with standard neonatal seizure protocols.[8] However, once the combination of primary microcephaly, feeding intolerance, growth failure, and minor limb (thumb) and facial anomalies became apparent on follow-up, it appropriately prompted exome sequencing rather than isolated CAH-focused work-up.

This sequencing strategy proved diagnostic and illustrates the increasing first-line role of exome sequencing in unexplained syndromic microcephaly, in keeping with published diagnostic yields for clinical exome sequencing in similar neurodevelopmental/dysmorphic cohorts.[1, 9] A firm diagnosis allows for anticipatory management of the recognised multisystem associations of CdLS- gastro-oesophageal reflux, growth failure, cardiac and ophthalmological anomalies, and neurodevelopmental delay- and enables informed genetic counselling for the family, including parental segregation testing given the X-linked dominant inheritance of CdLS5. [1, 4]

This report is limited by the absence, at the time of writing, of parental segregation studies to confirm whether the variant arose de novo or was inherited from a (potentially mosaic) parent, and by incomplete formal dysmorphology scoring against published CdLS clinical criteria.[1] Confirmatory Y-chromosome FISH and a comprehensive steroid hormone panel to definitively exclude an atypical steroidogenic defect were also pending at last follow-up.

5. Conclusion

Cornelia de Lange syndrome 5 due to *HDAC8* variants can present in the neonatal period with non-specific findings- a difficult perinatal transition, microcephaly, and atypical genitalia- that mimic congenital adrenal hyperplasia or disorders of sex development. A hormonal profile inconsistent with classic CAH, together with syndromic microcephaly on neuroimaging, should prompt early exome sequencing, which can secure a timely molecular diagnosis, guide multidisciplinary management, and inform genetic counselling for the family.

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