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Hydranencephaly and Bilateral Cleft Lip/Palate: Fowler Spectrum Expansion

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Abstract

To describe an unusual clinical case of hydranencephaly associated with complete bilateral cleft lip and palate, and to explore its possible relationship with Fowler syndrome, hypothesizing an expanded phenotypic expression of *FLVCR2*-related vasculopathy.

We report the case of a term male neonate with prenatal and postnatal diagnosis of hydranencephaly confirmed by computed tomography. A comprehensive clinical evaluation was performed, including conventional cytogenetic analysis and TORCH screening to exclude chromosomal and infectious etiologies.

The neonate presented with severe hydranencephaly and complete bilateral cleft lip and palate, without other evident systemic anomalies. Cytogenetic studies revealed a normal karyotype, and TORCH screening was negative. No relevant family history was identified. To our knowledge, this association has not been previously reported in the medical literature.

The coexistence of hydranencephaly and craniofacial malformations may represent an expanded phenotypic spectrum of Fowler syndrome or, alternatively, a distinct developmental vascular disorder affecting both cerebral and craniofacial arterial territories. This case highlights the importance of early vascular mechanisms in embryogenesis and supports further clinical characterization of rare congenital vasculopathies.

Keywords: Hydranencephaly; Fowler syndrome; cleft lip; cleft palate; congenital vasculopathy; neonatal neurology

Introduction

Hydranencephaly is a rare and severe congenital anomaly characterized by near-complete absence of the cerebral hemispheres, replaced by cerebrospinal fluid, typically resulting from early intrauterine vascular insults involving the internal carotid arteries (1–3). Its estimated incidence ranges between 1 in 10,000 to 1 in 20,000 births, although underdiagnosis may occur due to overlap with other destructive brain lesions.

The pathophysiology of hydranencephaly is primarily linked to bilateral occlusion or severe hypoperfusion of the internal carotid arteries during early gestation, leading to massive cerebral ischemia and subsequent destruction of supratentorial brain tissue (2,3). The posterior circulation, supplied by the vertebrobasilar system, is often relatively preserved, explaining the presence of brainstem and cerebellar structures.

Among the rare etiologies, Fowler syndrome represents a hereditary form of hydranencephaly associated with proliferative vasculopathy and mutations in the FLVCR2 gene (5,6,12). This gene encodes a heme transporter essential for endothelial cell function and vascular integrity. Mutations result in abnormal angiogenesis, vascular occlusion, and widespread ischemic damage during embryogenesis (6).

Cleft lip and palate are among the most common congenital craniofacial anomalies, with a multifactorial etiology involving genetic susceptibility and environmental factors (7–9). These malformations arise from failure of fusion of the facial prominences during early embryogenesis, a process highly dependent on adequate vascular supply.

Although both hydranencephaly and craniofacial clefts may share developmental timing, their coexistence has not been previously reported in the literature. This raises the possibility of a shared pathogenic mechanism, particularly involving early vascular disruption.

This report describes a neonate with hydranencephaly and complete bilateral cleft lip and palate, proposing a possible expansion of the phenotypic spectrum of Fowler syndrome or a broader congenital vasculopathy affecting both cerebral and craniofacial development.

Case Report

A male neonate was delivered at 37 weeks of gestation via cesarean section due to suspected fetal macrocephaly. Birth weight was 3700 g, length 50 cm, and head circumference was markedly increased (46 cm). Apgar scores were 6 and 8 at 1 and 5 minutes, respectively.

The mother had limited prenatal care, with incomplete follow-up. She reported exposure to unspecified medications during the first trimester and occasional alcohol consumption. No infections were documented during pregnancy, and there was no known consanguinity or relevant family history of congenital anomalies.

Prenatal ultrasound suggested severe ventriculomegaly, but no definitive diagnosis was established.

On physical examination, the neonate exhibited:

- Marked macrocephaly
- Wide fontanelles
- Generalized hypotonia
- Poor spontaneous movements

Craniofacial examination revealed:

- Complete bilateral cleft lip and palate
- Involvement of the premaxillary segment
- Midline facial abnormalities suggestive of disrupted craniofacial development

Neurological examination showed decreased primitive reflexes and generalized hypotonia.

Cranial computed tomography demonstrated a large bilateral fluid-filled cavity replacing nearly all cerebral hemispheres, with minimal residual parenchyma located posteriorly. The cerebellum and brainstem appeared relatively preserved. No intracranial calcifications or hemorrhage were identified.

Cytogenetic analysis revealed a normal karyotype (46,XY). TORCH screening, including cytomegalovirus, toxoplasmosis, rubella, and herpes simplex virus, was negative.

The patient was managed with supportive care. Due to the severity of neurological compromise, prognosis was considered poor.

Discussion

Vascular Pathophysiology of Hydranencephaly

Hydranencephaly represents the most severe form of fetal cerebral ischemic injury and is strongly associated with early disruption of the internal carotid circulation (1–3). The timing of vascular insult is critical; events occurring before 24 weeks of gestation typically result in extensive destruction of the cerebral hemispheres.

In Fowler syndrome, this process is driven by a genetically determined proliferative vasculopathy linked to FLVCR2 mutations (6). Endothelial dysfunction leads to abnormal vascular remodeling, luminal occlusion, and subsequent ischemia. The widespread nature of vascular compromise may extend beyond the brain.

Embryological Link to Craniofacial Development

Craniofacial structures develop between the 4th and 10th weeks of gestation through the fusion of facial prominences. This process is highly dependent on:

- Neural crest cell migration
- Adequate vascular supply
- Molecular signaling pathways

Disruption of blood flow to the frontonasal and maxillary prominences may impair tissue fusion, resulting in cleft lip and palate (7–9).

In the present case, the coexistence of hydranencephaly and bilateral cleft lip and palate suggests a **shared vascular mechanism**, potentially involving both internal and external carotid systems.

Expansion of Fowler Syndrome Phenotype

Fowler syndrome has traditionally been described as:

- Hydranencephaly or microhydranencephaly
- Fetal akinesia
- Arthrogryposis
- Pulmonary hypoplasia

Recent studies suggest that the phenotypic spectrum may be broader than initially recognized (6). The present case introduces a novel association with craniofacial malformations, supporting the hypothesis of a more diffuse embryonic vasculopathy.

This observation suggests that FLVCR2-related disorders may affect multiple vascular territories, including those involved in craniofacial morphogenesis.

Differential Diagnosis Several conditions should be considered in the differential diagnosis:

Condition	Key Features	Differentiation
Congenital CMV	Calcifications, microcephaly	Negative TORCH (17)
Adams-Oliver syndrome	Scalp defects, limb anomalies	Absent in this case (13)
Aicardi-Goutières syndrome	Encephalopathy, calcifications	No calcifications (14)
Dystroglycanopathies	Muscular involvement	Not present (15)
Mowat-Wilson syndrome	Facial dysmorphism, Hirschsprung	Not consistent (16)

The absence of infectious markers and normal karyotype strongly support a vascular etiology.

Broader Implications

This case reinforces the concept that early embryonic vascular disruption may represent a unifying mechanism linking:

- Severe cerebral malformations
- Craniofacial anomalies

Emerging evidence suggests that vascular integrity plays a central role in both neurodevelopment and craniofacial morphogenesis. Therefore, congenital vasculopathies such as Fowler syndrome may have broader developmental implications than previously recognized.

Limitations

A major limitation is the absence of molecular confirmation of FLVCR2 mutation. Advanced genetic testing such as whole-exome sequencing would be necessary to establish a definitive diagnosis.

Additionally, the lack of detailed prenatal imaging limits the ability to determine the precise timing of vascular insult.

Conclusion

This report describes a previously unreported association between hydranencephaly and bilateral cleft lip and palate.

The findings suggest:

- A possible expansion of the phenotypic spectrum of Fowler syndrome
- A broader embryonic vascular disorder affecting both cerebral and craniofacial development

Recognition of this association may improve understanding of early vascular mechanisms in congenital malformations and highlights the importance of genetic evaluation in similar cases.

Ethical Considerations

Written informed consent was obtained from the patient's legal guardians. The study was conducted in accordance with the Declaration of Helsinki.

Conflict of Interest

The authors declare no conflicts of interest.

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Author contributions (CRediT):

RVV: Conceptualization, methodology, research, formal analysis, original draft writing, review and editing, supervision.

LCC: Clinical management, research, resources, review and editing.

WRSL: Conceptualization, validation, review and editing, supervision.

AARS: Research, data curation, review and editing.

AEDC: Formal analysis, visualization, review and editing.

MVPI: Research, data curation, resources.

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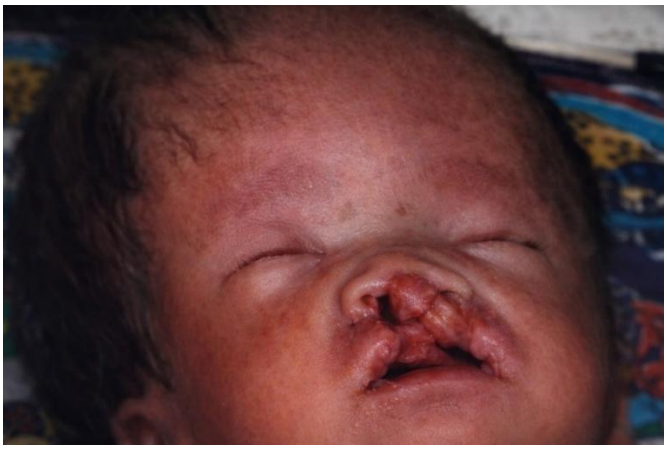
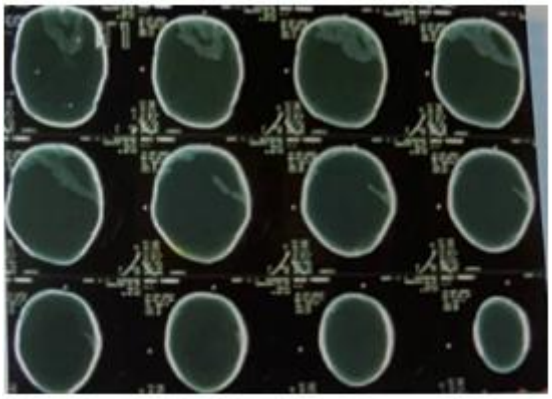
Annexes

Annexes 1.- notable macrocephaly is observed, with a prominent forehead and an increased cranial vault size in relation to the rest of the body. The ear is visible and appears to be normally positioned. The skin has a uniform coloration, without any evident lesions. Own experience. 2020



Annexes 2.- The image shows a close-up of the face of a newborn, in which apparent hypertelorism is evident, absence of normal nose formation, and a prominent structure in the midline of the nose, compatible with a mass or proboscis. No defined nostrils are observed. The forehead is wide and prominent, and the eyes seem to be closed, possibly with small or malformed palpebral fissures. Own experience. 2020



Annexes 3.- The image corresponds to a series of axial computed tomography (CT) scans of the skull, shown in radiological plate format. In the sections, there is a marked increase in the size of the cranial vault with frontal predominance, and an intracranial cavity almost entirely occupied by fluid (hypodensity), compatible with absence or marked reduction of supratentorial brain tissue, suggesting hydranencephaly or a major brain malformation. No defined cerebral ventricles or recognizable cortical structures are identified. Own experience. 2020

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