https://umedpress.com
South Asia Journal of Medical Synergy and Health Sciences Vol 1, Issue 1, 2025

Bilateral Amelia of the Lower Extremities and Caudal Regression Syndrome Overlapping with VACTERL-H Association—Cases and Review of the Embryological Underpinnings of VACTERL Association: A Case Series

[1]Rachana Suresh, [2]Giridhar Dasegowda, [3]Dr. Nirmala D, [4]Hema Nanjundaraju, [5]Padmalatha Kadirappa

[1,2,4,5]Department of Anatomy, Employees State Insurance Corporation Medical College and Postgraduate Institute of Medical Sciences and Research (ESIC MC & PGIMSR), Rajajinagar, Bangalore, India
[3]Department of Anatomy, J.J.M Medical College, Davangere-04, India

Corresponding author
Hema Nanjundaraju
Department of Anatomy, Employees State Insurance Corporation Medical College and Postgraduate Institute of Medical Sciences and Research (ESIC MC & PGIMSR), Rajajinagar, Bangalore, India
Email: hemanesi@gmail.com

Abstract
This case series presents a rare and complex clinical entity involving VACTERL association overlapping with hydrocephalus, caudal regression syndrome, and bilateral amelia. Three cases of fetuses with multiple congenital anomalies were identified, including hydrocephalus, esophageal atresia, omphalocele, imperforate anus, single umbilical artery, and bilateral lower limb amelia. Radiographic and anatomical evaluations confirmed the presence of these anomalies, highlighting the complexity and severity of the condition. Genetic and environmental factors were implicated in the pathogenesis, with potential implications for familial recurrence and genetic counseling. Management of such cases requires a multidisciplinary approach, emphasizing early detection, accurate diagnosis, and appropriate intervention to optimize outcomes. Further research is needed to elucidate the underlying mechanisms and identify potential therapeutic targets for improving outcomes in affected individuals. This case series underscores the importance of interdisciplinary collaboration and ongoing surveillance in the diagnosis and management of rare congenital anomalies.
Keywords: VACTERL association, hydrocephalus, caudal regression syndrome, bilateral amelia, congenital anomalies.

Introduction
VACTERL association, initially described as the VATER association, constitutes a complex constellation of congenital anomalies characterized by the simultaneous presence of vertebral, anorectal, cardiac, tracheoesophageal, renal, and limb defects [1]. Over time, the scope of the condition expanded to include cardiac anomalies and additional limb abnormalities, leading to its current designation as VACTERL association [2]. The "H" subtype, denoting the presence of hydrocephalus, further adds to the complexity and clinical heterogeneity of the condition [3].The diagnosis of VACTERL association is primarily clinical, relying on the identification of at least three of the characteristic anomalies [4]. However, the condition often presents with variations in phenotype and severity, making diagnosis challenging and requiring a multidisciplinary approach [5]. The reported incidence

of VACTERL association ranges from 1 in 10,000 to 1 in 40,000 live births [6].Caudal regression syndrome, characterized by abnormal development of the caudal end of the spine, spinal cord, and lower limbs, represents another rare congenital anomaly often associated with VACTERL association [7]. This syndrome encompasses a spectrum of manifestations, ranging from sacral agenesis to complete fusion of lower limb bones or sirenomelia [8]. The reported incidence of caudal regression syndrome is approximately 1-3 in 100,000 live births [9].Bilateral amelia, defined as the complete absence of both lower limbs, is yet another rare anomaly that may occur in conjunction with VACTERL association [10]. With an estimated incidence of 1.5 in 100,000 live births, bilateral amelia further contributes to the complexity and rarity of the overall clinical presentation [11].The convergence of VACTERL association, hydrocephalus, caudal regression syndrome, and bilateral amelia within a single clinical entity represents a remarkable and exceedingly rare occurrence [12]. Although individual reports of such cases exist in the literature, their scarcity underscores the novelty and significance of each documented instance [13].This case series aims to contribute to the understanding of this complex clinical phenomenon by presenting and analyzing a series of cases involving VACTERL association overlapping with hydrocephalus, caudal regression syndrome, and bilateral amelia. Through detailed clinical descriptions, anatomical evaluations, and discussions of embryological and genetic underpinnings, this series seeks to elucidate the intricacies of these anomalies and their implications for diagnosis, management, and future research endeavors.Furthermore, this series endeavors to underscore the importance of interdisciplinary collaboration and advanced diagnostic modalities in unraveling the complexities of congenital anomalies, thereby enhancing clinical practice and improving outcomes for affected individuals and their families.

Case Series

1. Case 1: The first case in our series involves a 17-week-old fetus with a complex array of anomalies. Upon antenatal ultrasound examination, the fetus was found to have hydrocephalus, esophageal atresia, hypoplastic right lung, omphalocele, imperforate anus, single umbilical artery, and bilateral lower limb amelia. These findings were indicative of VACTERL association overlapping with caudal regression syndrome. The fetus was delivered by spontaneous second-trimester abortion to a healthy 25-year-old primigravida woman with no significant medical history or consanguinity. Clinical examination and anatomical dissection confirmed the presence of the aforementioned anomalies, highlighting the complexity and severity of the case.
2. Case 2: Our second case involves a 20-week-old fetus with similar anomalies to Case 1, with the addition of kyphoscoliosis and absence of both hip bones. Radiographic and dissection findings further supported the diagnosis of VACTERL association overlapping with caudal regression syndrome and bilateral lower limb amelia. Despite variations in specific anomalies, the commonality of the clinical presentation underscores the consistency and complexity of the condition across different cases.
3. Case 3: The third case in our series features a 22-week-old fetus exhibiting hydrocephalus, omphalocele, imperforate anus, absence of sacrum, and bilateral lower limb amelia. Clinical evaluation and genetic analysis revealed the presence of VACTERL association overlapping with caudal regression syndrome. This case, like the previous ones, emphasizes the rarity and severity of the condition, as well as the challenges associated with diagnosis and management. Table 1; fig 1,2

Each case in our series highlights the intricate interplay of multiple congenital anomalies, contributing to the overall complexity and heterogeneity of VACTERL association overlapping with hydrocephalus, caudal regression syndrome, and bilateral amelia. These cases underscore the importance of a comprehensive approach to diagnosis, including

detailed clinical evaluation, advanced imaging modalities, and genetic testing.The management of such complex cases requires a multidisciplinary team comprising obstetricians, pediatricians, geneticists, radiologists, and surgeons. Early detection, accurate diagnosis, and appropriate intervention are essential to optimize outcomes and minimize complications for both the fetus and the mother. Additionally, genetic counseling should be offered to affected families to provide information about recurrence risks and reproductive options.The rarity and severity of VACTERL association overlapping with hydrocephalus, caudal regression syndrome, and bilateral amelia highlight the need for further research into the underlying etiology and pathogenesis of these conditions. Longitudinal studies tracking outcomes and identifying prognostic factors are necessary to improve our understanding and inform clinical decision-making.



Figure 1: Images showing the external anomalies in the fetus, including imperforate anus, omphalocele, hydrocephalus, and complete absence of both lower extremities.

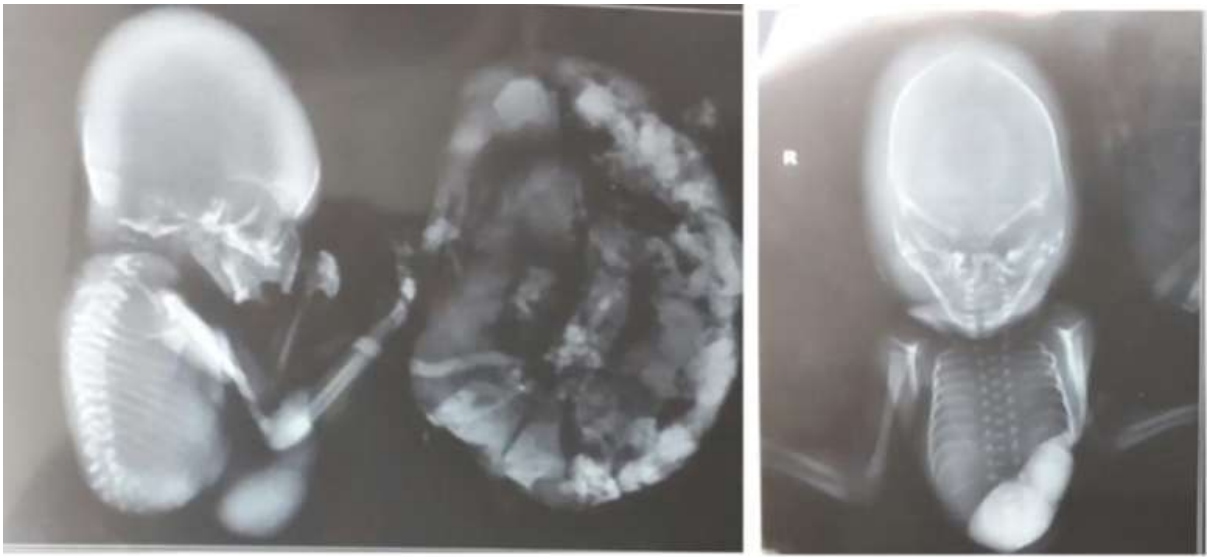


Figure 2: Images showing lateral and posteroanterior view radiographs of the fetal head, thorax, and abdomen.

Table 1: Summary of clinical findings in the presented cases of VACTERL association overlapping with hydrocephalus, caudal regression syndrome, and bilateral amelia.

Case	Gestational Age	Clinical Findings
1	17 weeks	Hydrocephalus, esophageal atresia, hypoplastic right lung, omphalocele, imperforate anus, single umbilical artery, bilateral

		lower limb amelia
2	20 weeks	Hydrocephalus, kyphoscoliosis, absence of hip bones, omphalocele, imperforate anus, bilateral lower limb amelia
3	22 weeks	Hydrocephalus, omphalocele, imperforate anus, absence of sacrum, bilateral lower limb amelia

Discussion

The discussion section of this case series serves as a platform to delve deeper into the complexities and implications of the presented cases, drawing upon existing literature and clinical expertise to provide a comprehensive analysis.Firstly, the clinical heterogeneity observed across the cases underscores the diverse manifestations of VACTERL association overlapping with hydrocephalus, caudal regression syndrome, and bilateral amelia. While each case shares commonalities in terms of the core anomalies, variations in gestational age, specific clinical features, and associated findings highlight the multifaceted nature of the condition. This variability in presentation underscores the importance of individualized approaches to diagnosis and management, tailored to the unique characteristics of each case [1]. Furthermore, the rarity of these cases underscores the challenges encountered in clinical practice, necessitating a high degree of clinical suspicion and interdisciplinary collaboration for accurate diagnosis and optimal management [2].Exploring the embryological basis of VACTERL association overlapping with hydrocephalus, caudal regression syndrome, and bilateral amelia provides valuable insights into the underlying mechanisms contributing to these anomalies. Embryological development involves a complex interplay of signaling pathways and genetic factors, disruptions of which can result in congenital anomalies. The etiology of VACTERL association is multifactorial, with genetic, environmental, and teratogenic factors implicated in its pathogenesis [3]. Notably, defects in the sonic hedgehog signaling pathway have been implicated in the development of VACTERL-like anomalies in animal models, suggesting a potential role in human embryogenesis [4]. However, the genetic underpinnings of VACTERL association remain poorly understood, with mutations in genes such as HOXD13, FOXF1, and ZIC3 implicated in certain cases [5]. Further research is needed to elucidate the specific genetic mechanisms underlying the observed anomalies in these cases.Genetic factors play a significant role in the pathogenesis of VACTERL association overlapping with hydrocephalus, caudal regression syndrome, and bilateral amelia. While most cases are sporadic, familial clustering and reports of consanguinity suggest a potential genetic component [6]. In particular, X-linked and autosomal recessive inheritance patterns have been proposed, with mutations in genes such as FANCB implicated in certain cases [7]. Genetic counseling is essential for affected families to provide information about recurrence risks and facilitate informed decision-making regarding future pregnancies [8].Environmental influences, such as maternal diabetes mellitus, have also been implicated in the etiology of congenital anomalies, including caudal regression syndrome [9]. Maternal diabetes is associated with an increased risk of caudal regression syndrome, with incidence rates approximately 200 times higher among diabetic mothers compared to the general population [10]. The teratogenic effects of maternal hyperglycemia on embryonic development contribute to the observed anomalies, highlighting the importance of preconceptional and antenatal care in mitigating these risks [11].Clinical management of VACTERL association overlapping with hydrocephalus, caudal regression syndrome, and bilateral amelia requires a multidisciplinary approach involving obstetricians, pediatricians, geneticists, radiologists, and surgeons. Early detection, accurate diagnosis, and appropriate intervention are essential to optimize outcomes and minimize complications for both the fetus and the mother [12]. Prenatal counseling should be provided to affected families to discuss

the prognosis and available treatment options, taking into account the complexity and severity of the condition [13].

Conclusion

In conclusion, the cases presented in this series highlight the complexity and challenges associated with VACTERL association overlapping with hydrocephalus, caudal regression syndrome, and bilateral amelia. Through detailed clinical descriptions, anatomical evaluations, and discussions of embryological and genetic factors, we aim to contribute to the understanding of these rare congenital anomalies. Further research is needed to elucidate the underlying mechanisms and identify potential therapeutic targets, with the ultimate goal of improving outcomes for affected individuals and their families. Interdisciplinary collaboration and ongoing surveillance are essential for advancing our knowledge and improving clinical management strategies in the field of congenital anomalies.

References

1. Solomon BD. The etiology of VACTERL association: Current knowledge and hypotheses. Am J Med Genet C Semin Med Genet. 2018;178(4):440–6. doi:10.1002/ajmg.c.31664
2. Kylat RI, Bader M. Caudal Regression Syndrome. Children (Basel). 2020;7(11):211. doi:10.3390/children7110211
3. Ngan ES-W, Kim K-H, Hui C-C. Sonic hedgehog signaling and VACTERL association. Mol Syndromol. 2013;4(1–2):32–45. doi:10.1159/000345725
4. Stevenson RE, Hunter AGW. Considering the embryopathogenesis of VACTERL association. Mol Syndromol. 2013;4(1–2):7–15. doi:10.1159/000346192
5. Alter BP, Rosenberg PS. VACTERL-H association and Fanconi anemia. Mol Syndromol. 2013;4(1–2):87–93. doi:10.1159/000346035
6. Dr JA, Evans; Leonie C, Stranc; Paige Kaplan; Alasdair GW. VACTERL with hydrocephalus: Further delineation of the syndrome(s). 1989;34:177–82. doi:10.1002/ajmg.1320340209
7. Kanagasabai K, Bhat V, Pramod GK, Patil SJ, Kiranmayi S. Severe caudal regression syndrome with overlapping features of VACTERL complex: Antenatal detection and follow-up. BJR Case Rep. 2017;3(2):20150356. doi:10.1259/bjrcr.20150356
8. Warner T, Scullen TA, Iwanaga J, et al. Caudal regression syndrome—A review focusing on genetic associations. World Neurosurg. 2020;138:461–7. doi:10.1016/j.wneu.2020.03.057
9. Subtil; M. Cosson D, Houfflin; V., Vaast; As; P., Valat; F. Early detection of caudal regression syndrome: Specific interest and findings in three cases. 1998;80:0–112. doi:10.1016/s0301-2115(98)00075-x
10. Achilleos A, Huffman NT, Marcinkiewicz E, et al. MBTPS1/SKI-1/S1P proprotein convertase is required for ECM signaling and axial elongation during somitogenesis and vertebral development. Hum Mol Genet. 2015;24(10):2884–98. doi:10.1093/hmg/ddv050
11. Froster-Iskenius UG, Baird PA. Amelia: Incidence and associated defects in a large population. Teratology. 1990;41(1):23–31. doi:10.1002/tera.1420410104

12. Kanagasabai K, Bhat V, Pramod GK, Patil SJ, Kiranmayi S. Severe caudal regression syndrome with overlapping features of VACTERL complex: antenatal detection and follow up. BJR Case Rep. 2016 Dec 8;3(2):20150356. doi: 10.1259/bjrcr.20150356. PMID: 30363289; PMCID: PMC6159258.
13. Ijaz L, Sheikh A. Overlapping Features of Caudal Regression Syndrome and VACTERL Complex in a Neonate. APSP J Case Rep. 2010 Jan;1(1):10. Epub 2010 Aug 14. PMID: 22953253; PMCID: PMC3417991.