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VACTERL-H syndrome

VACTERL is an acronym for a combination of congenital malformations of the **v**ertebrae, **a**nus, **c**ardiac tissue, **t**rachea, o**e**sophagus, **r**enal tissue and **l**imbs. This report describes the case of a preterm infant who was diagnosed with VACTERL associated with hydrocephalus (VACTERL-H). The features of VACTERL/VACTERL-H and the basic principles of diagnosis and management at birth are reviewed.

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Key points

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1. VACTERL-H is a rare expanded form of VACTERL that is associated with hydrocephalus.
2. Both autosomal recessive and X-linked inheritance have been described for VACTERL-H.
3. Fanconi anaemia is a major association of VACTERL-H.
4. VACTERL-H is associated with worse mortality and neurodisability than classical VACTERL.
5. Clinical management of affected infants at birth includes surgical correction of the defects as well as nutritional support measures pre- and post-operatively.

VACTERL-H is an expanded form of the VACTERL association. First described in the 1980s[1,2], it is characterised by congenital malformations of the vertebrae, anus, heart, trachea, oesophagus, renal system, limbs (VACTERL) and associated hydrocephalus (VACTERL-H). **TABLE 1** summarises the most common anomalies that are present in VACTERL association per body system. A diagnosis is based upon the presence of at least three component features plus hydrocephalus, provided there is no clinical or laboratory evidence of an alternative diagnosis[3]. There are case reports suggesting that central hypothyroidism is an additional component feature in the phenotypic spectrum of VACTERL-H[4,5]. A single umbilical artery may be an additional feature although the exact frequency of this feature cannot be estimated[3].

Case report

A male infant was born via an emergency caesarean section following induction of labour at 34 weeks' gestation for increased fetal head size and failure to progress. There was an antenatal diagnosis of polyhydramnios with tracheo-oesophageal fistula, progressively worsening bilateral brain ventriculomegaly and mild right renal hydronephrosis. The parents were not consanguinous and there was no history of abnormalities in their previous offspring.

At birth, the infant did not need resuscitation (Apgar scores of 9 at one and five minutes). Following transfer to the neonatal unit, he was breathing air and was started on intravenous 10% dextrose at a rate of 60mL/kg/day. Examination revealed a head circumference of 35.3cm (>99.6th centile) with an extra double thumb on the

	Features
Vertebrae	Hemivertebrae, butterfly vertebrae, wedge vertebrae, rib anomalies supernumerary vertebrae, vertebral fusions
Anus	Imperforate anus/anal atresia
Cardiac	Structural cardiac abnormalities (eg ASD, VSD, AVSD, PFO)
Trachea	Tracheo-oesophageal fistula
Oesophagus	Oesophageal atresia
Renal	Unilateral/bilateral renal agenesis, horseshoe kidney, dysplastic kidneys, ureteral anomalies
Limbs	Radial anomalies, thumb aplasia/hypoplasia, polydactyly, lower limb deformities
VACTERL-H	**Any three of the above plus hydrocephalus**

TABLE 1 Features of VACTERL and VACTERL-H.
Key: ASD = atrial septal defect, VSD = ventricular septal defect, AVSD = atrioventricular septal defect, PFO = patent foramen ovale.

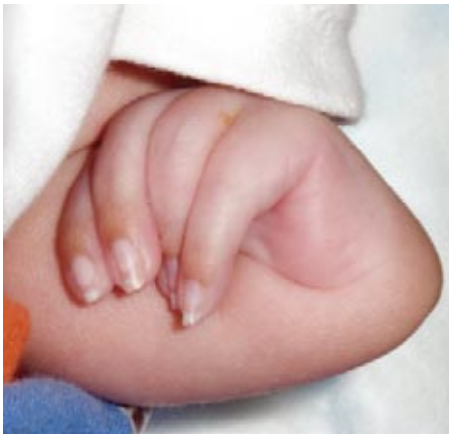

FIGURE 1 Left forearm malformation with radial aplasia.

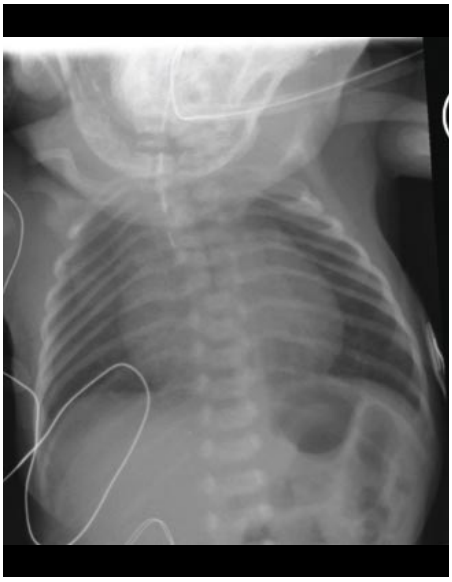

FIGURE 2 An anteroposterior (AP) chest X-ray following Replogle tube passage. The tip of the tube lies at the level of T5. A diagnosis of oesophageal atresia was confirmed.

right hand and radial aplasia on the left forearm (**FIGURE 1**).

A Replogle tube was sited in the oesophagus and a chest X-ray showed the Replogle tube tip lying at the level of T5 (**FIGURE 2**). The baby appeared to have 13 pairs of ribs and hemivertebrae were present at the level L4-L5. Based on these findings, a diagnosis of VACTERL association was made. Antenatal chromosome studies on samples from amniocytes revealed a normal 46XY male pattern and ruled out Fanconi anaemia. A cranial ultrasound on day three revealed an absent septum pellucidum and bilaterally enlarged ventricles. This was confirmed by magnetic resonance imaging (MRI) (**FIGURE 3**), which also revealed the absence of the corpus callosum. The cerebral aqueduct could not be visualised. A repeat renal ultrasound scan showed resolution of

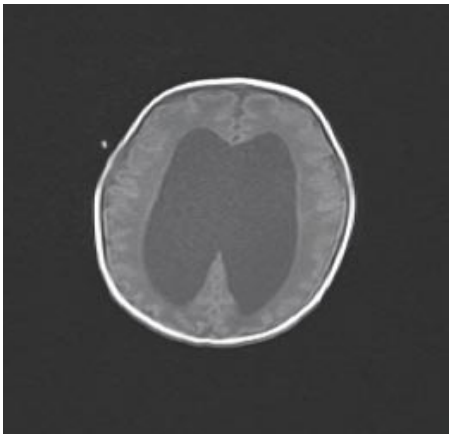

FIGURE 3 A brain MRI showing bilaterally enlarged ventricles with an absent septum pellucidum.

the antenatal hydronephrosis. A cardiac echocardiogram revealed a small patent foramen ovale (PFO)/patent ductus arteriosus (PDA) and possible muscular ventricular septal defects (VSDs).

The baby underwent surgical repair of the tracheo-oesohageal fistula and oesophageal atresia on day two. The fistula at the level of the carina was divided and closed, the ends of the two oesophageal pouches were brought together with moderate tension, a primary anastomosis was made and a transanastomotic tube (TAT) was placed. In the post-operative period, the infant failed extubation twice, due to increased oral secretions with airway compromise. A pre-extubation course of oral dexamethasone was given and the baby was extubated successfully onto bilevel positive airway pressure (BiPAP) on day 23 and was subsequently changed onto continuous positive airway pressure (CPAP) by day 28. Initially the baby received feeds with term formula milk via the TAT tube. The TAT tube was removed along with the endotracheal tube on day 23 and bottle feeds with specialised preterm formula milk were introduced. Episodes of aspiration were reported, which improved with a change of the formula milk and the introduction of ranitidine and domperidone. A barium swallow test revealed severe oesophageal dysmotility with reflux and a small stricture at the area of the previous anastomosis. Due to increasing head circumference, a ventriculoperitoneal shunt was inserted on day 41 of life.

On discharge, the infant was fully fed on thickened formula milk by bottle with additional feeds via a nasogastric tube. He required low flow oxygen via a nasal cannula. At the age of four months, there were no major visual concerns and his optic discs did not appear hypoplastic on fundoscopy. An orthopaedic referral was made to plan reconstructive surgery for the left radial aplasia.

Discussion

Aetiology

For the VACTERL association the estimated frequency is one in every 10,000 to 40,000 infants[3]. VACTERL-H is less frequently seen yet recognised as a distinct clinical entity; it has been reported in more than 50 patients[4]. The VACTERL-related anomalies are a result of a defect in mesodermal differentiation during early embryogenesis[6,7]. It is suggested that the pathogenesis of the syndrome can be explained on the basis of the 'developmental field complex' (DFC)[7] – the part of the embryo that responds as a coordinated unit to embryonic induction resulting in complex or multiple anatomic structures[8]. A disruption in the function of the DFC may result in multiple and sometimes distally located anomalies, such as the ones seen in the VACTERL association[6]. The presence of hydrocephalus in VACTERL-H is secondary to aqueductal stenosis, Arnold-Chiari malformation or non-progressive ventriculomegaly[9].

Genetic factors

There is evidence that genetic factors are associated with the development of the anomalies[3] however, the contribution of genetic factors in the development of VACTERL and VACTERL-H is different. Mutations in genes that have key roles in various signalling pathways have been implicated for VACTERL. The sonic hedgehog (*SHH*) signalling pathway plays a role in many processes during embryonic development[10]. Animals with mutations in genes associated with the hedgehog signalling pathway demonstrate features of VACTERL[3,10]. In humans, mutations or deletions in genes directly associated with hedgehog signalling (eg *FOXF1, HOXD13*) have been reported in patients with VACTERL-like phenotypes[10-12]. There have been some case reports of patients with VACTERL with concomitant mitochondrial dysfunction signs later in life, suggesting a potential genetic linkage[13,14]. Both X-linked and autosomal recessive forms have been described for VACTERL-H, which are clinically

indistinguishable[3,15]. There have been reports of sporadic patients with a VACTERL-H phenotype on whom a high rate of chromosomal breakage was observed[16,17]. Mutations in the Fanconi anaemia complementation group B gene (*FANCB*) have been associated with VACTERL-H[18]. Mutations in the *ZIC3* gene, which encodes a transcription factor that plays a key role in the left axis body formation, have been associated with a VACTERL-H phenotype. Ninety per cent of cases of VACTERL are sporadic with increased risk when there are multiple affected family members[3].

Associations

Fanconi anaemia is considered one of the major associations of the VACTERL-H syndrome. There is known phenotypic overlap with shared features such as radial abnormalities, hydrocephalus and other manifestations included in the VACTERL spectrum. Furthermore, as mentioned above, mutations in *FANCB*, which are known to cause Fanconi anaemia, have been associated with VACTERL-H[18]. A definitive diagnosis of Fanconi anaemia can be established by chromosome breakage studies on DNA obtained from blood or antenatally, from amniocytes.

Rhombencephalosynapsis is an uncommon cerebellar malformation characterised by fusion of the cerebellar hemispheres and the dentate nuclei. Abnormal formation of the fetal roof plate and the primitive cerebellar primordium result in various brain abnormalities such as holoprosencephaly, absent corpus collosum, neural tube defects and aqueduct anomalies. A morphological study of 40 fetuses with rhombencephalosynapsis, following medical termination of the pregnancy, revealed six cases of fetuses with VACTERL-H, suggesting a potential association between these two entities[19].

Caudal regression syndrome is a congenital malformation characterised by abnormal formation of the lower spine and sacral agenesis. The anorectal malformations seen in VACTERL have been suggested to be an overlapping feature with simultaneous occurrence of defects in distal anatomic sites[20].

Antenatal diagnosis

Antenatal diagnosis of malformations included in the VACTERL/VACTER-H syndrome is possible with the use of conventional ultrasonography or more sophisticated imaging techniques such as prenatal echocardiogram and MRI. Polyhydramnios and absent gastric bubble on the 20 week anomaly scan are highly suggestive of tracheo-oesophageal atresia/fistula. Distal colon dilatation is a sign associated with imperforate anus. Enlarged brain ventricles, bone and spine deformities can be ascertained with ultrasonography. The presence of a single umbilical artery should raise suspicion of VACTERL and lead to a careful antenatal examination for recognition of VACTERL anomalies. The diagnostic accuracy of antenatal ultrasonography depends on the experience and the skills of the ultrasonographer.

Management

The management of affected infants starts at birth with the surgical treatment of malformations that are incompatible with life. A colostomy is performed to treat an imperforate anus, followed by re-anastomosis and 'pull through' surgery. A tracheo-oesophageal atresia/fistula is treated with ligation of the fistula and anastomosis of the oesophageal pouches. Ventricular taps and ventriculoperitoneal (VP) shunting are used to release the increased intracranial pressure seen in hydrocephalus. Other anomalies seen in VACTERL/VACTERL-H can be treated surgically, depending on the nature of each malformation. Total parenteral nutrition (TPN) in the post-operative period is of major importance to ascertain nutritional support and stable growth until enteral feeds are fully established. Since most of the malformations carry a risk of long-term complications, a multidisciplinary team approach is followed to deal with post-discharge complications in the community.

Prognosis

During a 10-year follow-up period of infants with VACTERL, the estimated mortality rate was 24%, mainly due to cardiovascular abnormalities[22]. Prematurity and low birth weight are post-operative mortality risk factors[22]. Significant morbidity following repair of tracheo-oesophageal abnormalities has been reported due to increased incidence of complications such as oesophageal stricture and anastomotic leaks[21]. Anorectal and vertebral anomalies are associated with variable but poor functional outcomes in later life[21]. These outcomes have improved with the development of advanced surgical techniques and tertiary specialist centres[24]. Patients with VACTERL do not typically display neurocognitive impairment[3]. The prognosis for VACTERL-H is generally worse. There are only a few cases of infants surviving beyond infancy[23] and further studies are needed to evaluate their long-term outcomes.

Conclusion

Despite phenotypic similarities, there is evidence that the rare VACTERL-H syndrome is genetically distinct to the classical VACTERL association. With modern imaging antenatal diagnosis of the syndrome is possible. Fanconi anaemia is a major association of the syndrome and, when features suggestive of the syndrome are present on antenatal scans or at birth, chromosomal breakage studies should be considered to exclude the disorder. Along with surgical and nutritional management of affected infants, early geneticist involvement and genetic counselling is an essential part of the VACTERL/VACTERL-H care pathway.

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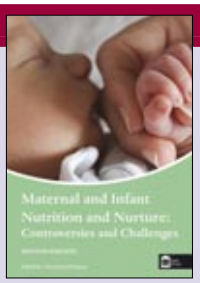
Book review

Maternal and Infant Nutrition and Nurture: Controversies and Challenges, Second edition



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Improved nutrition is increasingly seen as an achievable way of enhancing health outcomes for mothers and infants, both in the short and long-term. There are already many good books that examine this issue; finding space in a crowded market for another is not easy. Most of us work in an increasingly specialised area (eg preterm infants) and have a tendency to go for books relevant to our niche interests. It is always useful though, to see things from a different perspective.

Maternal and Infant Nutrition and Nurture is a book to read and browse, rather than a definitive source of text for, say, nutrient requirements. There are 10 chapters covering quite a diverse mix of subjects: from biology (antioxidant micronutrients in pregnancy) to practice (feeding preterm infants), and policy (breast milk substitutes) to psycho-sociology (nutrition in breastfeeding adolescents). When I first looked at the chapter titles I was a little confused – exactly who is this book aimed at? If I'm honest, I probably wouldn't have bought this book, but as I carried it around – it's small and easily fits into a day bag – I found myself dipping into a chapter here and there. I certainly came across perspectives or insights I wouldn't ordinarily gain.

Overall, it is well-written and well-referenced but more importantly, it has a readable style. I particularly liked the chapters on reasons why breastfeeding mothers weigh their babies and professional views on peer support for breastfeeding. One of the greatest shortfalls in current medical or nursing training is a lack of understanding of qualitative research methods, or a failure to see issues from anything other than a pure biomedical perspective. A wise professor once taught me that practitioners should be interested in social behaviours as well as cellular behaviours if we are to improve child health. This book gives a nice mix of both.

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