A case of congenital diaphragmatic hernia, limb-reduction defects and other abnormalities

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Congenital diaphragmatic hernias are usually an isolated finding, though other malformations and syndromes may also be present, including limb-reduction defects in up to 13.1% of infants. These defects often occur in the upper limb and on the ipsilateral side of the hernia. This association between congenital diaphragmatic hernias and limb-reduction defects suggests a developmental relationship, where both organs are either affected during the same embryological period or by the same factor/s (genetic and environmental/teratogenic).
Keywords. CDH; limb-reduction defects; congenital diaphragmatic hernia; sclerotome.

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Congenital diaphragmatic hernias (CDHs) are usually an isolated finding; however, other malformations and syndromes may also be present. The incidence of CDH varies between 0.8 - 5 per 10 000 births.[1] Van Dooren[2] identified a cohort of infants with CDH (Bochdalek type), of which 55.1% were isolated, 8.0% were associated with a chromosomal abnormality or syndrome and 36.9% had multiple congenital abnormalities. In that study, 13.1% of infants with a CDH had a limb-reduction defect (LRD), mostly in the upper limb and on the ipsilateral side of the hernia.[2] Martínez-Frías *et al.*[3] reported that in a cohort of malformed infants, 1.2% had a CDH. They also showed that some congenital defects were preferentially associated with CDH, with upper-limb deficiencies identified as one of the four specific patterns of preferential association.[3] In the group of infants with CDH and other congenital abnormalities, excluding syndromic infants, upper-limb deficiency was present in 3.2%.[3] The apparent association between CDHs and LRDs (with or without other congenital abnormalities or syndromes) has also been reported in other epidemiological studies and several case reports (references available on request).

Methods

Ethics approval and permission to publish this case report were obtained from the Research Ethics Committee at the Faculty of Health Sciences of the University of Pretoria (ref. no. 740/2018). A waiver of parental consent for the use of radiographic material was granted by the University of Pretoria ethics committee. This research complied with the ethical principles stated in the Declaration of Helsinki for medical research involving human subjects.

Case report

A late preterm female infant of 36 weeks' gestation was delivered via caesarean section to an HIV-negative 30-year-old woman from her fifth pregnancy. The newborn weighed 2 300 g and had a head circumference of 33 cm and a length of 43 cm. The Apgar scores were recorded as 4/10 at both 1 and 5 minutes, and she required resuscitation with intubation in the theatre. She had poor chest expansion despite positive pressure ventilation. Neurologically, she was encephalopathic and hypotonic, with absent primitive reflexes. Physical abnormalities present at birth were a right-sided shortened forearm, angulated wrist, syndactyly of the index and third finger and an absent thumb. The left hand had pre-axial polydactyly.

Relevant maternal obstetric history included one previous miscarriage and heroin use (opioid) during the current pregnancy. Prenatal ultrasound done 6 days before delivery raised a query of hydronephrosis of the right kidney.

The radiograph taken of this newborn demonstrated an upper limb-reduction defect of the right side (Fig. 1A and B), a large right-sided congenital diaphragmatic hernia with mediastinal shift to the left, situs inversus of the liver and complex vertebral and rib abnormalities (Fig. 1A). Additionally, there was pre-axial polydactyly of the left hand. Despite invasive ventilation, the newborn demised within 12 hours of birth, presumably due to severe pulmonary hypoplasia with pulmonary hypertension. A postmortem examination was not performed and, unfortunately, no ultrasound or karyotyping was performed. The absence of an ultrasound prevents us from determining whether this newborn had situs inversus totalis or situs ambiguous. However, with skeletal abnormalities, a diagnosis of VACTERL association (a combination of vertebral, anorectal, cardiac, tracheo-esophageal, renal and limb abnormalities) should also be considered.

Discussion

Approximately 45% of infants with CDH have other malformations or syndromes,[2] with upper and lower LRDs occurring in 3.2% and 2.1% of infants, respectively.[3] Additionally, Martínez-Frías *et al.*[3] reported combinations of vertebral and/or rib abnormalities in 3.2%, imperforate anus in 1.8%, cardiovascular abnormalities in 10.3%, oesophageal atresia in 1.4% and renal abnormalities in 6.4% of infants with CDH (non-syndromic infants). Similar to the infant in this case study, Van Dooren[2] describes two infants with features of VACTERL association in addition to their CDH and LRDs. Rittler *et al.*[4] reported that CDH occurs frequently enough in infants with VACTERL association to be deemed an 'extension' of the VACTERL association. Only two cases of situs inversus of

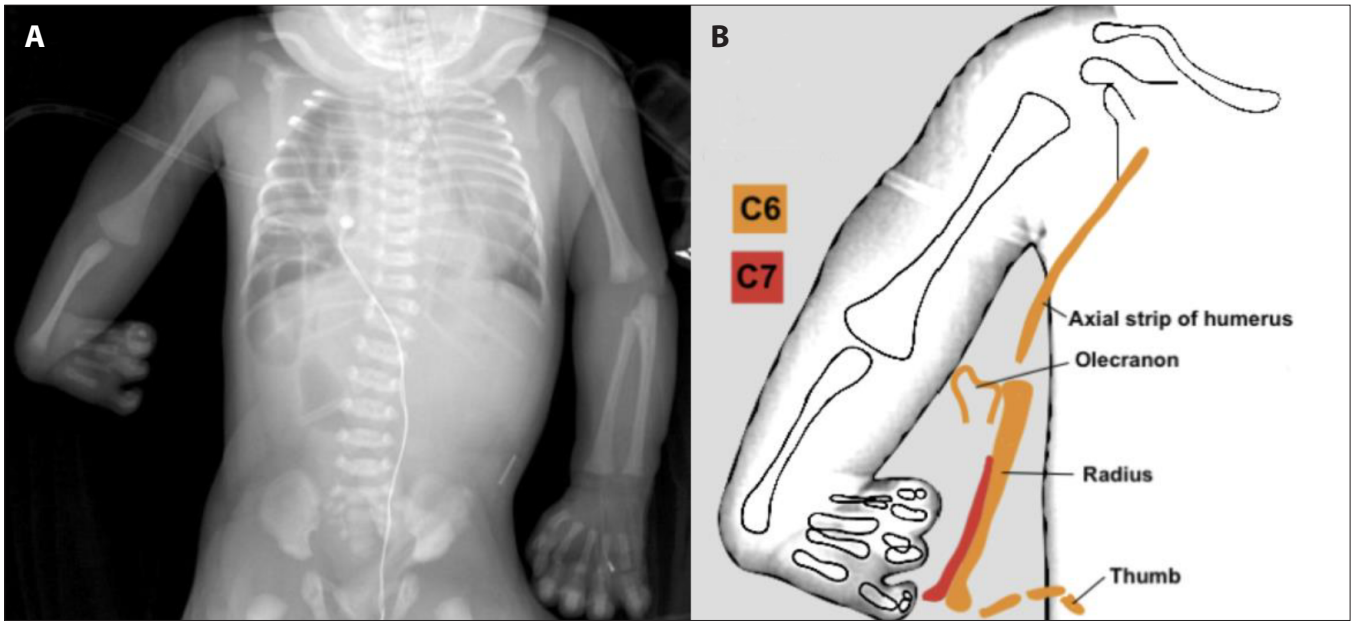

Fig. 1A. *Radiograph demonstrating right-sided congenital diaphragmatic hernia with an ipsilateral upper limb-reduction defect (reduced width of humeral shaft with flattened, flared distal end, shortened ulna with absence of the olecranon, absent radius, and an absent thumb). Pre-axial polydactyly on the left. Situs inversus of the liver is visible. Additional abnormalities of the ribs and vertebrae are present: thirteen ribs are well discerned on both the right and left, but mal-aligned and not symmetrically paired at all levels. The left-sided ribs start two vertebral levels above the right. Right side: Of the well-discerned ribs on the right, the first two are mildly hypoplastic compared with the corresponding ribs at the same level on the left, and the third is very hypoplastic as there is a corresponding hemivertebra on the left. The fourth rib is broad and the fifth is mildly hypoplastic. The fourth and fifth ribs both converge towards one vertebra. The sixth rib is located between two vertebrae. The eighth and ninth rib articulations with the vertebra are not well seen on the radiograph but appear to lead towards their respective vertebrae. Possible partial fusion of the right aspect of the vertebrae at the articulation of the twelfth and thirteenth ribs. Left side: The fifth rib arises off a hemivertebra. The eighth and ninth ribs are each located between two vertebrae.*

1B. *Sketch of 'sclerotome subtraction' as described by McCredie demonstrating the absence of bones (sclerotomes) in colour (method of representation adapted from McCredie 1999).*

abdominal organs with right-sided CDH have been published.[5,6] However, Martínez-Frías *et al*.[3] reports that polysplenia is present in 1.4% of cases of non-syndromic infants with CDH, which may represent a defect in laterality. Genes may act at different time points during development and cause defects/abnormalities of differing severity.[2] Similarly, the timing of an environmental insult may determine the combinations of organs affected and the severity thereof.[2] The relationship between the combination of congenital defects in this case is complex and likely multi-factorial. However, the occurrence of certain defects together may suggest a developmental relationship rather than a coincidence, as proposed by McCredie and Reid[7] in considering the combination of CDH with LRDs, where both organs are either affected during the same embryological period or by the same factor/s (genetic and environmental/teratogenic).[2]

McCredie and Reid[7] suggested that the sensory nervous system is involved in limb morphogenesis, noting a correlation between the segments of skeletal bones innervated by a single spinal sensory nerve (sclerotomes) and the morphology of skeletal malformations of the limbs. McCredie and Reid[7] hypothesised that failure of a trophic stimulus by the nerve supplying that organ would result in failure of that organ to grow, and used this hypothesis to explain the combination of CDHs with LRDs. The limbs and the diaphragm originate from somites adjacent to the cervical neural crest.[2] A single insult to the cervical neural crest segments during the sensitive period of limb and diaphragmatic development could theoretically result in malformations of both these organs through the failure of the trophic stimulus to the adjacent primordium, which is dependent on the sensory peripheral nervous tissue of the neural crest for its innervation.[7] This is supported by the overlap of the sensitive period of limb development (day 24 - 36 gestation) and diaphragmatic development (day 28 - 48 gestation).[7] An increased incidence of LRDs on the ipsilateral side to the CDH and the upper limb further supports this hypothesis.[2,7]

McCredie[7,8] showed that the segmental sensory nerve supply of the peripheral skeleton (sclerotomes) was mapped longitudinally, and an early insult resulted in a limb-reduction defect, termed 'sclerotome subtraction' (Table 1). The absence of one or more cervical sclerotomes in the upper limb resulted in the approximation of the remaining sclerotomes to the limb skeleton.[7,8]

The second theory suggests a genetic basis for both CDHs and LRDs, as several genes are involved in the development of both the diaphragm and the limbs.[2] In ~30% of cases of CDH, a genetic cause was identified, which includes aneuploidies, cytogenic rearrangements, copy number variants and single-gene mutations. Discordance of CDH in monozygotic twins suggests *de novo* mutations and the possibility of an epigenetic influence contributing to the development of CDH.[9] Although some chromosomal defects and Mendelian disorders display the co-occurrence of CDH and LRDs,[10] it remains unclear whether abnormal expression of genes is responsible for the combination of these defects in humans.[2] Further genetic studies are necessary to identify which genetic mutations are expected to cause an isolated defect (CDH) v. mutations that may affect multiple organs including the limbs.[9] A genetic basis for the abnormalities in this case may be plausible, given the wide range of congenital abnormalities present, in addition to the CDH and LRD.

Table 1. Diaphragm and upper limb skeleton with corresponding cervical somites and sclerotomes describing the radiological abnormalities with early insults resulting in diaphragmatic hernias and limb reduction defects ("sclerotome subtraction") [Table created from the text of reference 8]

Diaphragm	Cervical somites	Radiological abnormality
Posterolateral sections	C3 - C5	Diaphragmatic eventration or congenital diaphragmatic hernia (posterolateral)
Upper limb skeletal bones	**Cervical sclerotome(s)**	**Radiological abnormality**
Clavicle	C5	C5: Slightly shortened
Scapula	C5 - C7	C6: Slender, hypoplastic scapula
Glenoid	C6	Absent/small glenoid
Humerus	C5 - C8 (parallel axial strips) C6: Head, shaft, distal humerus, trochlea and capitulum C7: Epichondyles C8: Olecranon fossa	C6: Humeral head – small, flat-topped; humeral shaft – decreased bone mass of shaft (reduction in length of width); distal humerus, trochlea and capitulum – flat, flared distal humerus on a slender or short shaft, with lack of moulding of the joint surface
Ulna	C6 - C8 C6: Coronoid process and radial side of upper 1/3 posteriorly	C6: Hypoplasia or absence of coronoid process and radial side of olecranon
Radius	C6 - C7 C6: Upper and lower shaft C7: Lower shaft	C6: Absence of more than half of radial mass (shortening or narrowing), especially proximally. May have fusion of the distal radius to the distal ulna
Thumb	C6 and C7	C6: Absent or hypoplastic
Index finger	C6 and C7	C6: Slender and hypoplastic
Third finger	C7	C7: Absence
Forth finger	C7 and C8	C8: Absence or hypoplasia
Fifth finger	C8	C8: Absence

However, a specific genetic abnormality with VACTERL association in humans has yet to be found, although genetic contributions are suggested by familial reoccurrence and the high concordance in monozygotic twins.[11]

The third theory suggests that teratogens and vitamin A deficiency have been associated with CDH and/or LRDs in animal models.[2] When administered to pregnant rats, cadmium (heavy metal) resulted in a combination of CDH with LRDs, while nitrofen (herbicide) only caused CDHs in the offspring.[2] Severe vitamin A deficiency resulted in both CDHs and LRDs in various animal models;[2] however, the combination of CDH and LRD due to vitamin A deficiency has not been reproduced in human studies. Isotretinoin use during pregnancy has also been associated with limb-reduction defects in humans;[10] however, CDH was not associated with defects in these infants. Retinoic acid use during pregnancy has also been implicated in situs anomalies in offspring.[6] CDH with an associated LRD has been identified in one newborn with Rubella embryopathy.[2] Opioid use during pregnancy has not been consistently associated with various congenital malformations, as the increase in malformations is not statistically significant. Although CDH and limb-reduction defects occur with increased frequency in fetuses exposed to opioids, this relationship has also not been demonstrated to be significant.[12]

The combination of CDH and limb defects has been described as an isolated finding (n=5 cases), as part of chromosomal defects and Mendelian disorders, as part of other recognised patterns of multiple malformations and secondary to environmental factors.[10] Although Van Doorn[2] reported that LRDs are more common in the upper limb and on the ipsilateral side of the CDH, Evans,[10] in the 88 cases of CDH with LRDs, found no significant association between the sidedness of the defects (ipsilateral or contralateral) nor was there a significant association with upper-limb defects compared with lower limb defects. However, there was a trend towards ipsilateral limb and diaphragm defects in cases of Poland anomaly and cases of isolated CDH with limb defects.[10]

In patients with multiple congenital abnormalities, a genetic basis seems more likely. However, in patients with isolated CDH and LRD, McCredie's theory of an insult to the cervical neural crest during the sensitive period of both diaphragm and limb development may be plausible.

The case reported here demonstrates the co-existence of CDH with LRDs, particularly ipsilateral and affecting the upper limb. The additional abnormalities in this newborn—vertebral, rib, VACTERL association, abdominal situs inversus and possibly renal—have also been observed in infants with CDH.[2,3,5,6] The aetiology of the defects in this newborn is likely multifactorial. The combination of VACTERL association and isomerism in this case may represent a primary developmental field defect.[2,13] Although the combination of defects suggests a genetic aetiology, an environmental effect secondary to maternal heroin use cannot be excluded.

Declaration. None

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