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Deciphering caudal embryonic defects: embryological analysis and reviewing literature data

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Abstract

Background: A number of syndromes/associations involving the caudal region have been described in the literature. Each of them is characterized by a set of morphological features. Reports on difficulties in delineation and an ever-increasing constellation of defects in recent past call for a comprehensive study into the morphologic presentations and pathogenesis of caudal embryonic defects. *Materials and Methods*: The present article describes a case of the OEIS complex – a combination of omphalocele, exstrophy of bladder, imperforate anus and spinal defects. Literature search was performed and morphologic presentations, as described in literature, of all syndromes and associations affecting the caudal region of the embryo have been compared. Morphologic presentations were analyzed embryologically. *Results*: A remarkable overlap of symptom complex was observed. Embryological analysis of the phenotypic presentations of all these syndromes points towards a common pathogenesis, early in the embryonic life. The embryologic analysis suggests that these defects are a result of defects in proliferation, migration or subsequent differentiation of any of the three subdivisions of intra-embryonic mesoderm. *Conclusions*: Based on the analysis a new hypothesis for the causation of caudal defects is proposed. This hypothesis suggests that a local internal environmental imbalance, at the site of implantation, can cause nutritional insult to the embryo during gastrulation, during the third and the early fourth week of embryonic life.

Keywords: LBWC, gastrulation, sirenomelia, URSMS, VATER association.

Introduction

Carey JC *et al.* (1978) first described the combination of an omphalocele, exstrophy of the bladder, an imperforate anus, and spinal defects as the OEIS complex. The complex is quite rare and may have an incidence of 1 in 200 000–400 000 pregnancies [1]. The syndrome has also been described in monozygotic and dizygotic twins [2, 3]. It is also described as exstrophy of cloaca [4–6]. Over the years, after the identification of this complex, various communications have come up documenting a large spectrum of malformations associated with this complex [7–14]. The OEIS complex appears not to be so strongly restricted to the caudal part of the body and may also involve further cranial parts of the body [15].

A case of OEIS complex is being reported. While reviewing the literature, a striking similarity in phenotypic presentations was observed with other syndromes/associations like sirenomelia, VATER association, urorectal septum malformation sequence (URSMS), and limb body wall complex (LBWC) affecting the caudal region of the embryo.

Sirenomelia is characterized by a fusion and an abnormal rotation of the lower limbs. Associated anomalies include anorectal malformations, abnormal or absent genitalia, renal agenesis or cystic kidneys, spine and sacrum defects, preaxial anomalies of the upper limbs, as well as intestinal malformations and cardiopathies [16]. Caudal dysgenesis (CD) also referred to, in the literature, as caudal regression syndrome, combines caudal anomalies of varying degree and severity, involving the spine and the genitourinary system, with anorectal anomalies and pulmonary hypoplasia. Sirenomelia is considered to the worst form of caudal dysgenesis [16–19].

The VATER association was described more than three decades ago as a combination of three or more of these defects: (1) vertebral defects, (2) anal atresia, (3) esophageal atresia and/or tracheo-esophageal fistula, (4) renal dysplasia, and (5) radial-ray limb anomalies [20].

Escobar LF *et al.* (1987) introduced the term URSMS when describing six female patients with urogenital malformations [21]. According to Wheeler PG *et al.* (1997), the syndrome can be divided into full and partial types, concerning the severity of the disease spectrum. Full URSMS, the most severe form, includes the absence of perineal and anal orifices, ambiguous external genitalia, abnormal internal genitalia, and renal agenesis/dysplasia [22]. In partial URSMS, a single perineal/anal opening drains a common cloaca, in combination with an imperforate anus. URSMS has also been associated with cardiac, gastrointestinal, vertebral, and limb anomalies.

The presence of body wall defects (usually lateral) with evisceration of thoracic and/or abdominal organs (thoraco- and/or abdominoschisis), limb deficiency, and myelocystocele, is considered a limb body wall complex [23, 24].

With the increase in the number of cases being reported, a wider spectrum of malformations is being documented in these syndromes/associations. There have been reported cases in the literature where, clear deli-

neation of a particular syndrome has not been possible and overlap of two or more syndromes or associations is seen [25–32]. Present study compares the phenotypic presentations and performs an embryological analysis of syndromes involving the caudal region of the embryo.

Materials and Methods

A case of OEIS complex sent to the Department of Anatomy was embalmed. Available clinical history of the mother of the fetus was obtained from the hospital records. Dissection of the fetus was performed to observe and document the external and internal anomalies. To obtain published literature on various birth defects involving the caudal region of the embryo, a thorough literature search was performed in all major biomedical databases. The caudal birth defects were identified as: (1) OEIS complex [1, 2, 7–9, 11–15, 33, 34], (2) sirenomelia [18, 19, 35–41], (3) VATER association [20, 42–46], (4) URSMS syndrome [21, 22, 47–49], and (5) limb body wall complex [23, 24, 50–57]. For the embryological analysis of phenotypic presentations, articles were selected using following criteria: (1) there should be no reported ambiguity in identification or delineation of syndrome/association, (2) reports with multiple cases or retrospective review/studies of multiple cases were included, (3) cases reporting novel phenotypic presentations of a particular syndrome/association. Along with criteria 1 (which was the essential criteria) any one of the other two criteria were used for selection of the article. The phenotypic presentations described in the published articles were then categorized into various systems and then analyzed embryologically. The embryological analysis was intended to trace the causation of the birth defects to its genesis during embryogenesis.

Results

Case: OEIS complex

A 35-year-old female delivered a still-born baby at 20 weeks of pregnancy. No history of any chronic or acute clinical condition or any drug intake was documented. The female had a history of abortion at 16 weeks in her first pregnancy, full-term normal delivery with a surviving 7-year-old child from second pregnancy, and an intrauterine death at full-term in the third pregnancy. No further details about previous three pregnancies were available.

External appearance

Large defect was observed in anterior abdominal wall. Coils of intestines, liver, kidneys, urinary bladder and uterus herniated out from the defect. The herniated contents were covered by membrane (Figure 1). The perineum showed a central elevation, suggestive of genital tubercle. No external anal opening or pit was seen. External genitalia were absent. A skin tag, of the size of a lemon seed, was observed at the commencement of free lower limb. No external defect was visible in the back. Both the lower limbs were malrotated laterally by 90^0, so that the ventral aspect of both lower limbs faced dorsally and vice versa (Figure 1). Talipes equinovarus of the left foot was present. Ears were low set. No cleft lip or palate was observed. Radiography revealed lumbosacral spinal defect.

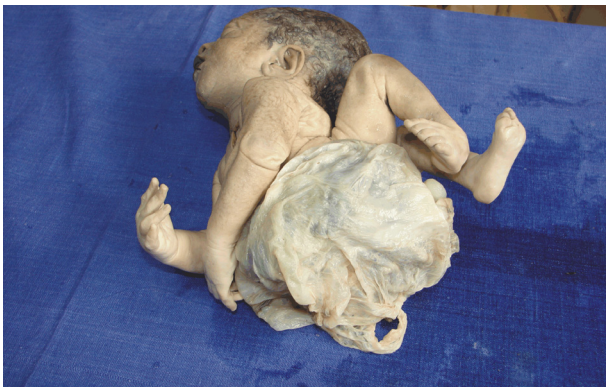

Figure 1 – ***Fetus with OEIS complex. Large omphalocele and malrotated lower limbs are visible.***

Dissection findings

Thorax

Lungs, heart, the great vessels and the thymus gland were normal. No defect was observed in the diaphragm.

Abdomen and pelvis

Esophagus, stomach with its ventral and dorsal mesentery, duodenum and pancreas were normal. Spleen was normal and was present in the dorsal mesentery of the stomach. Liver showed presence of multiple cysts in both right and left lobes. Gallbladder was normal. Patent left umbilical vein was present in the falciform ligament. The small intestine continued into a muscular sac, which ended blindly. A septum separated this sac from urinary bladder, which was a hollow muscular sac exposed to the exterior. No trigone and urethral opening could be identified in the bladder. Right kidney was normal but the right pelvis and the ureter were dilated, coiled and continued into the urinary bladder (Figure 2).

Figure 2 – ***Right kidney (k), ureter (u) and bladder (b) of fetus with OEIS complex. Intestine (i) is seen ending in a blind sac (s) which is separated from the bladder by a septum.***

Left kidney was cystic with no pelvis and ureter. Suprarenals appeared normal bilaterally. A muscular structure suggestive of uterus with a deficient posterior wall was present. Single fallopian tube, on the right side

was observed. Gonads were absent. Presence of spina bifida with lipomeningomyelocele was seen in the lumbosacral region (Figure 3).

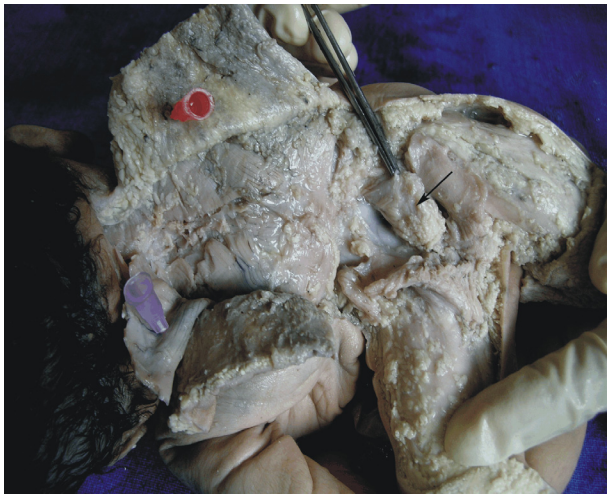

Figure 3 – ***Fetus with OEIS complex. Meningomyelocele in the lumbosacral region.***

Dorsal aorta continued as a single umbilical artery on the left side (Figure 4). Inferior vena cava and portal vein were absent. A plexus of veins drains the abdominal organs and walls. Umbilical cord had two vessels – a single umbilical artery and a vein. The artery was continuation of left umbilical artery; vein continued into the falciform ligament.

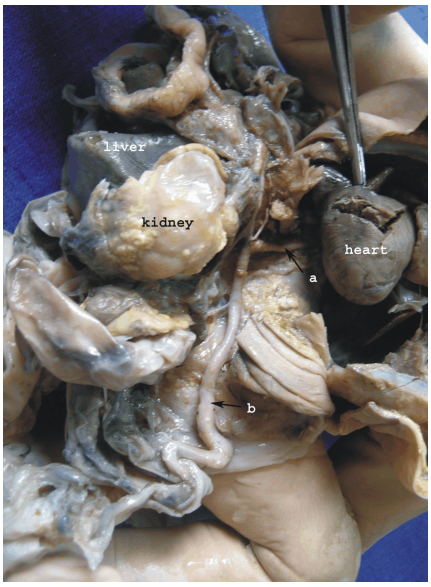

Figure 4 – ***Fetus with OEIS complex. Dorsal aorta (arrow – a) continuing as left umbilical artery (arrow – b).***

Embryological analysis

Table 1 shows a comparison of phenotypic and morphologic presentations of various syndromes/associations affecting the caudal region of the body as reported in the literature, including that of the present case. The table also shows the embryologic analysis of these presentations. A considerable overlap of symptoms of different defects described in the caudal region of the embryo is evident from the Table 1.

Table 1 – ***Morphologic anomalies/defects described in various syndromes/associations affecting the caudal region of the body and their embryologic analysis***

Anomaly/ Defect	OEIS	Sirenomelia	VATER	LBWC	URSMS	Embryologic analysis
Limb anomalies	Fusion of digits	Polydactyly, fusion of digits	–	Polydactyly	–	Inappropriate apoptotic signals in limb bud mesoderm – somatopleuric mesodermal defect.
	Lower limb fusion	Lower limb fusion	–	–	–	Tail fold deformity due to faulty signals in the caudal region of the embryo, resulting in migration of lower limb buds and fusion with one another to variable extent – somatopleuric mesodermal defect.
	Lower limb deficiency	Hypoplastic, malformed, absent lower limb	Deformations, pre-axial limb anomalies, radial dysplasia	Limb defects	Limb anomalies present	Tail fold deformity due to faulty signals in the caudal region of the embryo results in defective/absent limb buds – somatopleuric mesodermal defect.
Vertebral anomalies	Kyphoscoliosis, partial or complete sacral agenesis	Scoliosis, hemivertebrae, sacrococcygeal agenesis	Axial skeletal defects	–	Lumbosacral vertebral defects	Defective sclerotomal migration around the notochord (might be secondary to faulty signaling from the notochord – para-axial mesodermal defect.
	–	Rib anomalies, iliac, ischial, pubic bone dysplasias	Rib anomalies	–	–	Defect of somatopleuric mesoderm in the thoracic wall.
Abdominal wall defects	Omphalocele	Omphalocele	Gastroschisis	Thoraco-abdomino-schisis	–	Failure of formation of anterolateral body wall due to faulty signaling of somatopleuric layer of mesoderm.
	Exstrophy of bladder/ cloaca	–	Exstrophy of bladder/ cloaca	Exstrophy of bladder/ cloaca	Exstrophy of bladder/ cloaca	Failure of formation of infra-umbilical part of abdominal wall due to defective somatopleuric layer of mesoderm. As a result, the cloacal membrane remains ventral in position and its breaking down results in exstrophy of bladder (if the urorectal septum is formed) and exstrophy of cloaca (if the urorectal septum is deficient).

Anomaly/ Defect	OEIS	Sirenomelia	VATER	LBWC	URSMS	Embryologic analysis
Gut anomalies	Esophageal, duodenal atresia	Esophageal, ileal atresia	Esophageal, small intestinal atresias	–	–	Atresias are a result of vascular disruption of any part of intestine rather than being a primary defect.
	Anal atresia, imperforate anus	Anal atresia, imperforate anus	Anal atresia, imperforate anus	Anal atresia, imperforate anus	Anal atresia, imperforate anus	Cloacal membrane not ruptured because the mesoderm moves in between the endoderm and the ectoderm – defect of improper migration of caudal somatopleuric mesoderm.
Neural tube defects	Spina bifida – lumbosacral	Spina bifida – lumbosacral	Spina bifida – lumbosacral	–	–	Sclerotomal migration defect (paraxial mesoderm) due to faulty signal or due to faulty notochordal induction or secondary to meningomyelocele.
	Meningo-myelocele	Meningo-myelocele	Hydrocephaly	Meningo-myelocele hydrocephaly	–	Due to faulty induction by notochord or secondary to spina bifida.
	–	Cranio-rachischisis totalis	–	–	–	Sclerotomal migration defect due to faulty signal or due to faulty notochordal induction.
External genitalia	Ambiguous, absent genitalia	Ambiguous, absent genitalia	Ambiguous genitalia	Ambiguous, absent genitalia	Ambiguous, absent genitalia	Faulty migration and proliferation of mesoderm around the cloacal membrane (somatopleuric mesoderm).
Gonads	Absent	Absent	–	Absent		Derived from nephrogenic cord – intermediate mesodermal defect.
Perineal openings	Imperforate anus	Imperforate anus	Imperforate anus	Imperforate anus	Imperforate anus	Cloacal membrane not ruptured, mesoderm moves in between the endoderm and the ectoderm, defect of improper migration of caudal somatopleuric mesoderm.
	–	Single perineal opening	–	–	Single perineal opening	Persistence of a common cloacal chamber opening through a single opening due to urorectal septum malformation defect – a defect of splanchnopleuric mesoderm.
Urinary system	–	Renal agenesis UL/BL	Renal dysplasia	–	Renal agenesis, renal dysplasia	Nephrogenic chord defects – intermediate mesodermal defect.
	Polycystic kidney	–	–	–	Polycystic kidney	Failure of mesonephric tubules to join mesonephric duct (absence of ureter may also be there) – mesonephric duct not formed – intermediate mesodermal defect.
	Agenesis of urethra or bladder	Agenesis of urethra or hypoplastic or absent urinary bladder	–	Agenesis of urethra or bladder	Agenesis of urethra or bladder	Persistence of a common cloacal chamber, failure of urorectal septum formation, defect of splanchnopleuric mesoderm.
Diaphragmatic defects	–	–	Present	Agenesis of diaphragm	Agenesis of diaphragm	If associated with body wall defect – somatopleuric layer of mesoderm; or failure of fusion of different contributions from somatopleuric and splanchnopleuric layers.
Cranio-facial defects	Didicocephaly, cleft lip, cleft palate	–	Cleft lip/palate eye and ear defects	Cranial disruption by bands, cleft lip and palate	–	Craniofacial defects are essentially defects of neural crest mesenchyme and represent a simultaneous disruption in the formation of head and neck mesenchyme.
Cardiovascular defects	–	Tetralogy of Fallot	ASD, Tetralogy of Fallot, TA	–	VSD	These defects are essentially defects of inter-atrial or inter-ventricular or aortico-pulmonary septum which are contributed by mesenchyme derived from neural crest mesenchyme.
Respiratory system defects	–	–	Tracheo-esophageal fistula	–	Tracheo-esophageal fistula	Defective formation of tracheo-esophageal septum – defect of neural crest mesenchyme.
Single umbilical artery	Present	Present	Present	Present	Present	–

It is also evident that analysis of causation of the phenotypic defects can be traced to the early embryonic life as a defect in formation, migration or differentiation of any one subdivisions of intra-embryonic mesoderm (*i.e.* paraxial mesoderm; intermediate mesoderm and lateral plate mesoderm) or of the mesoderm formed by the neural crest cells.

Discussion

The present case presented with all characteristic features of the OEIS syndrome. The clinical diagnosis in the present case was abdominal wall defect *i.e.* omphalocele. It was only after the dissection, that the diagnosis of this syndrome could be ascertained. Keppler-Noreuil K *et al.* (2007), in their report of 15 cases and a review of 20 cases, concluded that it was difficult to diagnose the full extent of anomalies prenatally, despite several criteria being proposed for the diagnosis. Subsequently, the syndrome remains under-reported [11].

There have been reported cases of difficulty in delineation because of overlapping features of two syndromes/associations [9, 25, 28–31, 45]. The confusion in nomenclature is rising as more and more number of cases, with larger spectrum of anomalies and overlapping features keep being reported. Epidemiological studies can provide an answer to this. However, there exists some difference of opinion about the delineation of these defects in epidemiological studies [6, 15, 58, 59]. The limitations of the epidemiological studies are obvious, as the full spectrum of disorder is often not documented. Furthermore, there is a tendency to classify the birth defects with-in the described syndromes/ associations.

The present study is comprehensive and has taken into account all the birth defects involving the caudal region. The study demonstrates that phenotypic presentations of all caudal defects overlap considerably.

A review of literature suggests that different hypothesis have been put forward for causation of the caudal defects.

Pathogenetic mechanisms

Various pathogenetic mechanisms proposed:

- For OEIS: polytopic-field combination defects [29]; single blastogenesis defect [60]; genetic contribution [2] and embryologic field defect of mesodermal migration at about 29 days [8].
- For sirenomelia: vascular steal hypothesis (which asserts that blood flow through the aberrant vessel is diverted from the caudal embryo's developing structures) [61], and a combination of vascular disruption, mesodermal injury, and defective micro-perfusion [38] were regarded as causal mechanisms of sirenomelia earlier; more recently, caudal mesodermal defect [18] developmental field defects [19] were suggested as causative mechanisms.
- For VATER: axial mesodermal dysplasia spectrum [62], chromosomal imbalances [63].
- For URSMS: alterations in sonic hedgehog and homeobox genes lead to caudal mesodermal deficiency during blastogenesis [22, 55, 56].
- For LBWC: a primary rupture of the amnion [24]; vascular disruption of embryonic tissue [50, 53]; disturbance of the embryonic folding process [64].

As is apparent from the above discussion various hypotheses have been put forward for the pathogenesis of these associations. In an excellent analysis of several birth defects, Opitz JM traced the causation to blastogenesis (blastogenesis encompasses all events beginning from karyogamy until day 28) [60, 65].

However, the ambiguity persists regarding specific questions 'when', 'why' and 'how' do these defects occur. Few molecular or experimental data exists on causes of blastogenetic defects in humans.

Gastrulation errors

Gastrulation is a process by which the bilaminar embryonic disc is converted to trilaminar embryonic disc. It is the beginning of morphogenesis and is significant event occurring during the third week. Gastrulation begins with the formation of primitive streak at about fifteenth day of embryonic life. The primitive streak is a midline proliferative region of the epiblast where the cells may break free from the epithelium and migrate beneath the epiblast to form the intra embryonic mesoderm [66, 67]. Gastrulation errors can be explained as errors in proliferation, migration and subsequent differentiation of the intra-embryonic mesoderm resulting in defective morphogenesis.

The embryologic analysis in Table 1 suggests that the defects are a result of involvement of all the three subdivisions of the intra-embryonic mesenchyme (*i.e.* para-axial, intermediate and lateral plate) and the notochord. Since the craniofacial mesenchyme is mainly derived from the neural crest [66], the defects involving cranial regions and the cardiovascular system can be categorized as defects of neural crest mesoderm.

The present embryological analysis pins down the causation of these defects to the third and early fourth week of the embryonic life, during the process of gastrulation. The phenotypically different associations or defects can be subsets of a common error of gastrulation. The phenotypic presentation depends on the number of developmental fields affected, their combinations, and the precise time at which the process of gastrulation is affected.

Understandably, the complex process of gastrulation is sensitive to insult from genetic and environmental influences. Therefore, gastrulation errors can be result of: (a) inherited gene defects and (b) defects under the influence of environmental factors which manifest in the form of altered gene expression. The varied constellation of associations, overlapping with other associations, favors environmental factors. The presentation of the defects depends on the time and the extent of involvement of the expression of a single or multiple genes responsible for single or multiple developmental fields. This hypothesis also accounts for expression of the association in monozygotic and dizygotic twins, where the two developing embryos share similar local environments.

Role of environmental factors in gastrulation errors

Environmental factors can again be classified into intrinsic and extrinsic. Intrinsic factors include the local environment around the developing embryonic disc (*i.e.* uterine endometrium and the cavities of the embryo).

In first week of life, the blastomeres derive their nourishment, in part, from stores laid down in the

cytoplasm of the primary oocyte and from tubal and uterine secretions [68]. In second and third week of life, the embryonic disc is dependent on nutrients obtained from the fluid filled cavities of the amnion, the celom and the yolk sac. These fluids contain products arising because of absorption by the trophoblast from the lysed uterine tissues and extravasated maternal blood. However, these sources of supply are much diminished and inadequate at an early stage in development. It therefore becomes imperative that some other source should be available at an early stage. This involves formation of placenta and establishment of fetal circulation. By the end of the third week, the primitive cardiovascular system is established and the heart begins to beat so that the blood now circulates [66].

Thus, the third week of fetal life is a challenging period, when a transition of source of nutritional supply to the developing embryo is taking place. During the third week, the existing nutritional supply starts diminishing and the fetal circulation is yet to start. Incidentally, it is the same period when gastrulation process is going on. The diminishing supply of nutrients is bound to affect the deeper tissues (mesoderm) more than the layers towards the fluid filled cavities (the ectoderm and the endoderm) and hence the vulnerability of the mesoderm. Support to this hypothesis comes from the fact that increase in the incidence of multiple congenital malformations is recognized in the children of diabetic mothers [69]. It is known that diabetes causes tissue starvation and hence the uterine endometrium is unable to provide optimal nutritional support. Experimental studies, specially looking into the nutritional insult to the embryo, at the time of gastrulation, are required to substantiate this hypothesis. However, the practical difficulties in carrying out such studies are also well known [70].

Although often discussed as a cause [67] the extent to which the extrinsic factors *e.g.* alcohol, smoking, medication, toxins can affect the embryo at this stage is also a matter of investigation, because extrinsic environmental factors come into play only after placentation and the establishment of fetal circulation resulting in intimate contact of the embryo with the maternal blood.

The second most favored hypothesis – the vascular hypothesis, states that the defects are a result of vascular disruption, leading to incomplete development of embryonic tissue due to hemorrhagic necrosis and anoxia (of already formed embryonic tissue). It is known that all mesenchymal tissues angioblastic cells [71]. The ultimate position of the endothelial vessels is believed to be patterned by the mesenchymal populations of the neural crest in the head, somatopleuric mesenchyme in the limbs and splanchnopleuric mesenchyme around the viscera [66]. Therefore, the altered vascular supply is a result of defective mesenchymal population, rather than its cause. All other hypothesis suggested, seem to be the effects of early gastrulation errors, rather than being the causes of respective associations.

The present investigation highlights some important facts. The full extent of the associations may not be documented prenatally and an autopsy is recommended to document the full spectrum of disorders whenever possible. There is a considerable overlap of presentations of associations affecting the caudal region of the body, which points towards a common pathogenesis. A larger constellation of symptom complex points towards an insult, early in embryonic life. Nomenclature of the syndromes/associations may preferably be made on embryologic basis rather than phenotypic presentations. The syndromes/associations discussed should be preferably categorized as gastrulation errors. The phenotypically different associations or defects can be subsets of a common error of gastrulation.

Conclusions

The most important outcome of the present analysis is identification of a vulnerable period during gastrulation. Based on the analysis a new hypothesis for the causation of caudal defects is proposed. This hypothesis suggests that a local internal environmental imbalance, at the site of implantation, can cause nutritional insult to the embryo during gastrulation, during the third and the early fourth week of embryonic life. Experimental studies are required to substantiate the above hypothesis. The results of such studies will also be beneficial in assisted reproductive technology.

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