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Case Report
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Caudal Regression Syndrome – Example of Structural Malformation with Normal Karyotype after IVF

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Abstract

Introduction: Caudal Regression Syndrome (CRS) is a syndrome of unknown pathogenesis characterized by multiple anomalies involving genitourinary system, anorectal anomalies, defects in caudal part of vertebral column and various anomalies of lower extremities.

Case Report: We present the case of CRS which is the first case of this syndrome after *in vitro* Fertilization (IVF) to the best of our knowledge. Female patient age 40, who suffered from hyperthyroidism and was on Propylthiouracil (PTU) therapy, was treated for secondary infertility and had undergone IVF and Embryonic Transfer (ET). In the 13th week of pregnancy cell free DNA test was performed due to nuchal translucency measurement of 2.9 mm, which showed no abnormalities. In the week 18 sonographic examination showed multiple fetal anomalies affecting mainly the caudal part, accompanied by decreased fetal movements with preserved upper extremity movements. Also, Single Umbilical Artery (SUA) was detected.

Conclusion: Numerous theories regarding pathogenesis of CRS have been proposed. Two of them - vascular steal theory and possible dysfunction of caudal mesoderm – have gained most attention. However, pathogenesis of CRS remains incompletely understood. Possible connection between IVF or PTU therapy and CRS development should be taken into account until proven otherwise.

Keywords: Caudal regression syndrome; Structural malformation; *In vitro* fertilization; Propylthiouracil

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Introduction

Caudal Regression Syndrome (CRS) or Caudal Dysgenesis (CD) is a syndrome characterized by multiple anomalies involving genitourinary system, anorectal anomalies, defects in caudal part of vertebral column and various anomalies of lower extremities. More benign cases of CRS can present in the adulthood with minor abnormalities, such as chronic constipation and congenital anal stenosis [1]. Incidence of CRS varies between 1:20 000 and 1:100 000 [2]. Both sexes are equally affected [3]. First description of the syndrome was given by Duhamel in to 1961 [4]. More than half a century later both CRS remains incompletely understood clinical entity.

Case Presentation

Here we present the case of CRS which could be additional contribution in deepening our understanding of this serious set of anomalies. To the best of our knowledge this is the first case of CRS which developed after IVF.

Female patient age 40, who has previously undergone uterine septum resection, was treated for secondary infertility. She suffered from hyperthyroidism and was taking Propylthiouracil (PTU). According to family history there were no previous fetal malformations. Infertility was treated with *in vitro* Fertilization (IVF) and Embryonic Transfer (ET) into our patient's uterus. At 13th week of pregnancy, cell free DNA test was performed in order to clarify nuchal translucency measurement of 2.9 mm which was detected. The test result was completely normal. At 18th week of pregnancy sonographic examination revealed multiple fetal anomalies affecting mainly caudal body part. Decrease in fetal movement was detected, with preserved upper extremity movements. Continuity of vertebral bodies was interrupted at lower thoracic/upper lumbar level. Lumbar vertebrae were dysplastic and sacral vertebrae were not observed. There was clear asymmetry of pelvic bones (Figure 1). Lower extremities were immobile and close to Buddha or frog position. Clubfoot was

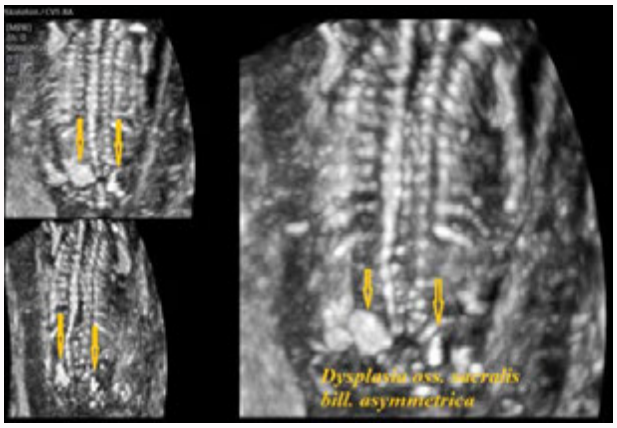

Figure 1: 3D ultrasound image showing bilateral dysplasia and asymmetry of pelvic bones.

present bilaterally. Intestines were hyperechogenic and imperforate anus was suspected. Single Umbilical Artery (SUA) was detected. Head circumference was normal and no ventriculomegaly was observed. Normal, four-chambered heart was observed. Diaphragm and stomach were normally positioned. Kidneys and filled urinary bladder were visualized.

Altogether these anomalies were consistent with caudal regression syndrome. Finally, parents chose to terminate the pregnancy at 18th week.

Discussion/Conclusion

Number of authors have reported cases of CRS without any remarkable family history or parental consanguinity [3,5]. Only maternal diabetes has been proposed as risk factor [6]. Some of the well-known consequences of the Assisted Reproductive Technology (ART) are multiple gestations, preterm labor, lower birth weight and chromosomal anomalies. However, it is still debatable if ART causes higher incidence of structural congenital anomalies when compared to general population [7]. Our finding could point into direction of potential relationship between IVF and congenital anomalies.

Two main theories regarding pathogenesis have been developed – vascular steal theory [8] and caudal mesoderm dysfunction. Kozlowski et al. assume possibility CRS could be part of general bone dysplasia [5]. It remains debatable if sirenomelia and caudal dysgenesis have two different pathogenic pathways or do they represent different stages of the same disorder. Additional theory suggesting malfunctioning of notochord inductive pathways has been proposed [6]. Moreover, case of Junctional Neural Tube Defect (JNTD) has been described in which patient presented with stigmata closely related to those seen in CRS, such as sacral agenesis, hypertonic anal sphincter, bilateral clubfeet, urinary incontinence and atrophy of lower extremities muscles. Consequently, authors suggested impaired secondary neurulation, which is proposed basis for JNTD, could be pathogenic origin of the caudal regression syndrome [9]. We believe that further research of secondary neurulation defects could shed new light on pathogenesis of CRS.

Furthermore, Retinoic Acid (RA) signaling appears to play significant role in the CRS pathogenesis. Retinoic acid, vitamin A derivative, is a signaling molecule that regulates gene transcription, cell cycle and proliferation, differentiation and organogenesis through the interaction with the nuclear receptors, Retinoic Acid Receptor (RAR) and Retinoid X Receptor (RAX) in autocrine, cell autonomous manner and also in non-cell autonomous, paracrine manner by diffusing across cell membranes establishing retinoic acid gradients within and across tissues [10,11]. In placental species, lipophilic RA is manufactured from maternal diet-derived retinol (vitamin A) during embryogenesis. After entering the cell, retinol is reversibly oxidized to retinal by alcohol dehydrogenase and Retinol Dehydrogenase (RDH), particularly RDH10. Retinal is then irreversibly converted to RA, particularly all-trans Retinoic Acid (atRA), which is catalyzed by Retinaldehyde Dehydrogenase (RALDH) enzymes, especially RALDH2 [11]. It has a great impact on both axis formation (anterior and caudal truncations) and neural differentiation. Under normal conditions of embryonic development, embryo is protected against fluctuations of maternal dietary RA concentration. This highlights the importance of CYP26 genes, which when mutated aren't able to degrade dietary RA and as a result abnormal phenotype occurs. Null mutations for CYP26a1 in mouse resulted in missing posterior vertebrae (lumbar, sacral and caudal), thoracic vertebrae were often deformed, 20% of embryos expressed sirenomelia due to hindlimb fusion, while some exhibited malpositioning of hindlimbs [11]. PTU, as a known hepatotoxic drug, could also interfere with ability of CYP enzymes in the liver to degrade RA and hence expose fetus to higher levels of maternal RA.

As far as we know this is the first case of CRS associated with maternal hyperthyroidism and PTU therapy. Question remains whether hyperthyroidism, PTU therapy or iatrogenic hypothyroidism could exert teratogenic effect and lead to CRS development. PTU was shown [12] to decrease RAR and RXR levels in the mice. If the same mechanism is applicable to humans, then it can be assumed that higher concentrations of unbound retinoic acid in the mother's serum could cross the placenta and cause teratogenic effects in the embryo/fetus.

So far, no serum marker for CRS has been proven as useful, unless it is complicated with open Neural Tube Defect (NTD) in which case higher AFP serum levels can be measured [13]. Ultrasound is a mainstay of antenatal diagnosis. Alongside ultrasound, MRI has proven useful in diagnosing CRS [14]. In the case of CRS associated with NTD, which was described previously [15], it is of uttermost importance to diagnose the condition as early as possible. In utero myelomeningocele surgery before 26th week of pregnancy was shown to result in better neurologic outcome when compared to standard postnatal procedure [16]. Same could be true for myelomeningocele associated with CRS. Sonographic evidence of hydrocephalus or specific sonographic signs such as "lemon sign" and "banana sign" suggest NTD or Chiari malformation is present [17]. CRS without NTD does not usually involve hydrocephalus as was shown in our case.

Associations of CRS with different kinds of anomalies has been described, such as annular pancreas [2], diastematomyelia [15], cleft lip [18] and extrahepatic biliary atresia [19]. It remains to be elucidated if there is pathogenic common ground for all of these malformations. Hence, we propose every patient diagnosed with CRS should be carefully evaluated in order to define full extent of malformation.

It seems likely that still unknown noxious factor affects caudal region of embryo/fetus. Namely, from our case report and all other cases described so far it is evident that tissues from all three germinative layers are affected. Our case adds additional evidence that

hypoperfusion theory could be true as fetus was shown to have SUA. Findings in our case disprove previously proposed thesis according to which SUA is abnormality commonly associated with sirenomelia instead of CRS [18].

Nomenclature in the literature regarding CRS is confusing. Different authors describe syndrome using different names. Some authors discard name "caudal regression syndrome", as they do not believe something that has normally developed regresses but development itself is dysfunctional. Terms "sacrococcygeal agenesis" and "sacral agenesis" have also emerged as possible for naming the syndrome [19,20]. Clear sonographic parameters for diagnosis of CRS would definitely clarify situation. Four-type classification of CRS which correlates with prognosis has been suggested [20].

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