CASE REPORT

Prenatal diagnosis of caudal dysplasia sequence associated with undiagnosed type I diabetes

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SUMMARY

Caudal regression or caudal dysplasia sequence (CDS) is a rare congenital malformation, which includes a wide spectrum of musculoskeletal abnormalities involving the lumbosacral spine, pelvis and lower limbs. It can be associated to visceral defects in various degrees. Maternal diabetes, genetic predisposition and vascular hypoperfusion have been suggested as possible causative factors. Women with diabetes who are dependent on insulin are 200–400 times more likely to have a child with caudal regression, making CDS the most characteristic fetal abnormality of diabetic embryopathy. Prenatal diagnosis is possible by ultrasonographic examination. The sonographic findings include abrupt interruption of the lumbar spine and 'Buddha or frog position' of the lower limbs. MRI has demonstrated the level of the vertebral anomalies as well as the associated abnormalities and this is crucial because the prognosis of this condition depends on the severity of the lesion and the presence of associated disorders.

BACKGROUND

We have had the opportunity to perform a thorough work-up with very beautiful images because it is a rare congenital malformation.

CASE PRESENTATION

We report a 24-year-old pregnant woman in her first pregnancy with onset of type I diabetes mellitus with diabetic ketoacidosis at 6 weeks of gestation. At that time haemoglobin A1c (HbA1c) was 13% and fasting blood glucose level was 379 mg/dl. She was on insulin glargine 28 UI daily, insulin lispro 7-7-7 UI plus a 2000 kcal diet. Insulin pump therapy was initiated. The autoimmune work-up showed: glutamic acid decarboxylase autoantibodies (GAD-65) >120 nmol/l (normal 0–5), tyrosine phosphatase-related islet antigen 2 (IA-2) antibodies 106 nmol/l (normal ≤0.02 nmol/l) and C-peptide level 0.77 ng/ml (normal 0.5–2.0 ng/ml). In the first blood test for prenatal control an autoimmune sub-clinical hypothyroidism was also detected and that is why a hormone replacement therapy was started with thyroxine at 75 µg/day. At 8+5 weeks of gestation HbA1c level was 11.6% and this is why dosing of insulin glargine was increased to 30 UI. At 13+6 weeks of gestation blood glucose levels were normal. At that time the patient showed no hypoglycaemia and was on insulin glargine 30 UI plus insulin lispro 7-7-7 UI. At 18+6 weeks of gestation HbA1c was 6.5%, blood glucose controls were normal and no hypoglycaemia were reported. The patient continued with the same therapy.

INVESTIGATIONS

An ultrasonography scan at 12 weeks of gestation showed 1 week discrepancy in fetal crown-rump length. A follow-up examination at 21 gestational weeks showed a sudden termination of spine at lumbar level (figure 1) and fixed lower extremities with right clubfoot. Lower limb movements were absent during all the examination. The lower extremities crossed each other in a 'frog-like' position. No other anomalies were seen and the amniotic fluid volume was normal. A four-dimensional scan allowed showing parents the scope of orthopaedic anomalies (figure 2). In order to complete the diagnosis, a MRI and a fetal karyotype were performed. The karyotype was 46 XY. MRI showed the absence of the last lumbar vertebral bodies and sacrum (figure 3), confirming the suspicion of caudal dysplasia sequence (CDS). Genitourinary or otherwise anomalies associated were not visualised.

DIFFERENTIAL DIAGNOSIS

Diagnostic considerations based on prenatal imaging included sirenomelia, neural tube defect and body-wall complex.

TREATMENT

Once parents were informed about the severity of the malformations of their baby, they decided to terminate pregnancy.

OUTCOME AND FOLLOW-UP

The woman delivered a 430 g male baby without any complication. The fetus was referred for pathological examination which confirmed the MRI findings.

DISCUSSION

CDS is characterised by a series of congenital abnormalities, including complete or partial agenesis of the sacrum and lumbar vertebrae associated with pelvic deformity. Femoral hypoplasia, clubbed feet and flexion contractures of the lower extremities are also commonly seen. Additionally CDS is often associated with anomalies of the gastrointestinal and genitourinary tract and heart, as well as with neural tube defects.^{1–6}

The incidence of this syndrome is approximately 0.01–0.05/1000births, but in pregestational mothers with diabetes CDS can occur in 0.3–1% of infants.^{6,7}

The precise mechanism leading to CDS is unknown. Defective development of caudal embryo elements, originating from the midposterior axial mesoderm, before the seventh week of gestation, is probably the common pathway.^{1–4,7}

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Figure 1 Two-dimensional ultrasound scan showing absence of sacrum.

To our knowledge, the exact aetiology leading to the development of CDS has not been established. Diabetes, particularly with poor glycaemic control, as in our patient, is certainly the most recognised risk factor, since the risk for CDS in such patients is as high as 1–2%, compared with 1:60 000 in the general population.^{1–4 8} However, history of maternal diabetes is present in only 16–22% of infants with CDS.^{5 6}

Congenital anomalies are known to be related to poor maternal glycaemic control in the early weeks of pregnancy, the period of organogenesis.⁹ The passage through the placental barrier of maternal insulin is not possible and fetal insulin is not produced before the eighth week of development, so the embryo is especially vulnerable to hyperglycaemia insult during this period.^{1 3 5} High blood glucose levels are thought to cause congenital abnormalities by inhibiting glycolysis, the primary process of energy production during embryogenesis.³ It has also been hypothesised that hyperglycaemia leads to release of free radicals; these excess free radicals can be teratogenic.⁵

Figure 2 A four-dimensional scan showing lower extremities crossed each other in a 'frog-like' position.

However, Zaw *et al* reported a case of CDS affecting only one of a set of monozygotic twins, born to a mother with diabetes. This case suggests that the aetiology cannot be fully explained by the environmental influence only. Genetic factors should also be considered.^{5 8} In patients with autosomal dominant sacral agenesis a homeobox gene (HLXB9) has been identified as a major causative gene. Although the link between homeobox genes and CDS-induced diabetes has not yet been established.^{1 5}

The clinical manifestations of the CDS include neurological anomalies (segmental deficit corresponding to the level of vertebral agenesis, predominantly motor impairment with relative sparing of the sensory function), orthopaedic anomalies (deformities of the pelvis: hip dislocation or dysplasia, narrow

Figure 3 MRI showing absence of the last lumbar vertebral bodies and sacrum.

pelvic region and deformities of the lower extremities: frog-leg position, clubfeet). Genitourinary and/or gastrointestinal manifestations are associated with these anomalies.^{1 2 4 6 8}

A prenatal ultrasonographic diagnosis of CDS is possible. The diagnosis can be made as soon as 9 weeks of pregnancy with high-resolution transvaginal ultrasonography. Baxi *et al* reported a case of suspected CDS at 9 weeks gestation: a shortening of the crown-rump length and a protuberance of the lower spine suggested CDS. By 17 weeks of gestation the diagnosis was made with certainty.¹⁰ The characteristic ultrasound findings include abrupt interruption of the spine at the dorsal or lumbar level and abnormal position of the lower limbs. The femur bones are fixed in a 'V' pattern, giving a typical 'Buddha's poise'. Ultrasound can also be helpful in diagnosing associated congenital malformations.^{2 7 4 8 11}

The prognosis depends on the extent of spinal abnormalities; the greater the extent of spinal anomalies, the greater the neurological deficits. And it also depends on the presence of associated abnormalities.⁷

Accurate and early counselling to the parents is crucial, to enable rational decision-making.

Prenatal diagnosis focuses on discerning the extent of CDS. Three-dimensional skeletal mode is particularly helpful when skeletal defects are present and can help both, to make a more accurate diagnosis.²

The use of MRI, although not essential, can help assess fetal anatomy. As Stroustrup, we think that if this diagnostic tool is available it can help to complete the diagnosis and provide reassurance to parents. MRI effectively depicted the level of vertebral agenesis and, therefore, enables adequate diagnosis not only of the anomalies of the spine, but also of most of the associated anomalies in the pelvic region.^{3 6}

Diagnostic considerations based on prenatal imaging included sirenómelia, neural tube defect and body-wall complex.^{3 7}

There is some evidence that preconception counselling and careful diabetic control in the preconceptional period and the first 8 weeks of pregnancy may lower the chances of congenital anomalies.⁵

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Learning points

- This case report shows the importance of a very good periconceptional metabolic control in those women with known diabetes. We strongly encourage primary care providers to discuss with these women the consequences of maternal diabetes mellitus as part of routine anticipatory guidance for antenatal management.
- Ultrasound findings are quite characteristic and allow early diagnosis.
- We suggest a high-resolution scan at 16–17 weeks of gestation for early detection of diabetic embryopathy, particularly in patients with poor periconceptional glycaemic control.
- We recommend the use of other imaging techniques (MRI or three-dimensional ultrasound), in the event that they are available, to confirm the diagnosis and determine the extent of the injury.

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