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CASE REPORT

Caudal Regression Syndrome with Partial Agenesis of the Corpus callosum and Partial Lobar Holoprosencephaly

Case report

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متلازمة النكوص الذيلي مع نقص التكوّن الجزئي للجسم الثفني وانْدِمَاجُ مُقَدَّم الدماغ الفصي الجزئي

تقرير حالة

هلال الهشامي، ماريا باتاكلان، مريم ماثيو، لاليثا كرشنان

الملخص: متلازمة النكوص الذيلي حالة جنينية نادرة الحدوث في الحمل المصاحب بداء السكري . وعلى الرغم من أن الآلية الدقيقة لحدوث هذه الحالة غير معروفة. لكن ارتفاع سكر الدم أثناء تكوين الجنين يبدو هو المسؤول . ومن جهة اخرى فقد تم وصف متلازمة النكوص الذيلي وعدم التكون للجسم الثفني واندماج مقدم الدماغ الفصي الجزئي - بصورة منفردة - لأجنة الأمهات المصابات بسكر الحمل. وعلى حد علمنا فإن الجمع بين كل هذه الحالات مع بعضها لم يتم الإبلاغ عنها لحد الآن.

مفتاح الكلمات: داء السكر في الحمل، متلازمة النكوص الذيلي، اِنْدِمَاجُ مُقَدَّمِ الدِّماغ، الجِسْمُ الثَّفَنِيُّ، تقرير حالة، عُمان.

ABSTRACT: Caudal regression syndrome is a rare fetal condition of diabetic pregnancy. Although the exact mechanism is not known, hyperglycaemia during embryogenesis seems to act as a teratogen. Independently, caudal regression syndrome (CRS), agenesis of the corpus callosum (ACC) and partial lobar holoprosencephaly (HPE) have been reported in infants of diabetic mothers. To our knowledge, a combination of all these three conditions has not been reported so far.

Keywords: Diabetes in pregnancy; Caudal regression syndrome; Holoprosencephaly; Corpus callosum; Case report; Oman.

Incidence of congenital malformations is three to four times more common in infants of diabetic mothers than in the general population. These include neural tube defects, anomalies of the heart, urogenital system, skeleton and alimentary tract, and the caudal regression syndrome (CRS). Caudal regression syndrome is characterised by variable lumbosacrococcygeal or sacrococcygeal agenesis. It is accompanied by symmetrical multiple musculoskeletal anomalies of the pelvis and legs in babies of mothers with diabetes mellitus;[1] however, genetic predisposition and vascular hypoperfusion have been suggested as other causal factors.[2] Agenesis of the *corpus callosum* and holoprosencephaly has also been described as a component of diabetic embryopathy.[3] A rare combination of all these three conditions in an infant of a diabetic mother is reported here.

Case Report

A baby boy was born at 38 weeks gestation to a 28 year-old, gravida 6, mother of a non-consanguineous marriage. Her previous five babies were normal. She was diagnosed to have Hodgkin's lymphoma in 2005 and was in remission at the time of this report. When diagnosed with lymphoma, she was also detected to have diabetes and has been on insulin since that time. The glycaemic control of the mother was poor in the first trimester with a high level of haemoglobin A1C (HbA1C) of 11.6% at 8 weeks of gestation. The control improved subsequently

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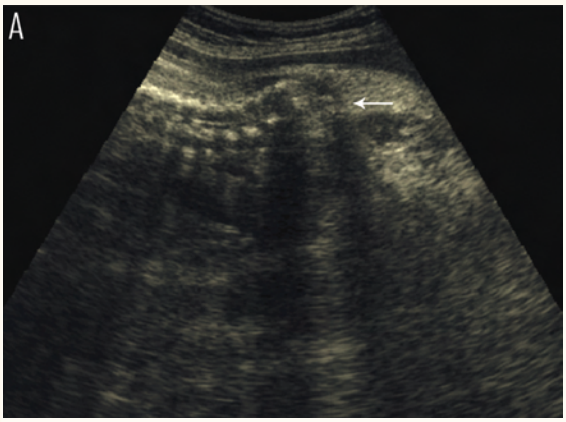

Figure 1a : Antenatal ultrasound scan of the fetus at 24 weeks showing abrupt termination of the lumbar spine (arrow)

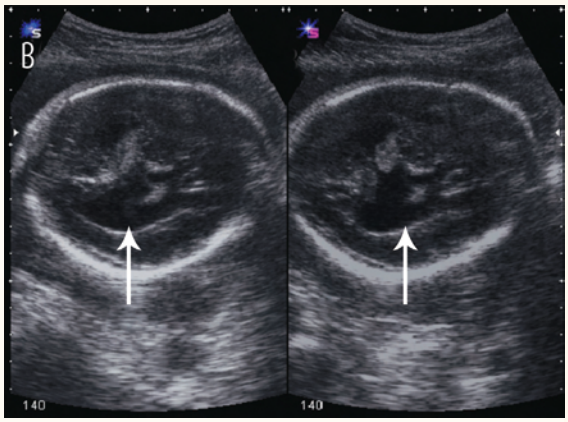

Figure 1b. Bilaterally dilated lateral ventricles with absent septum pellucidum (arrows)

with a drop in HbA1C to 9.5% at 20 weeks and 6.5% at 32 weeks, (the recommended value during pregnancy is <6%). An antenatal scan of the fetus at 24 weeks showed abrupt termination of the lumbar spine with bilateral club feet and bilaterally dilated lateral ventricles with absent *septum pellucidum* [Figures 1a and 1b]. The baby was born by elective cesarean section for breech presentation at 38 weeks gestation. His Apgar score was 8 at one minute and 9 at 5 minutes. The birth weight was 3610 g (90th percentile for gestational age [GA]); his head circumference 36 (90th percentile for GA). Physical examination of the lower limbs showed muscle wasting below the hips. There were dimples on the lateral aspect of both thighs overlying the greater trochanters and also over the bony prominence in the lower spine. The hips were flexed and adducted with fixed hyperextension of the knees. The femoral bones assumed a V-shaped position [Figures 2a and 2b]. Dribbling of urine was noticed on the second day of birth with a poor urine stream. The anus was patulous.

The baby had transient tachypnea requiring nasal continuous positive airway pressure. The neonatal period was otherwise uneventful. His skeletal survey showed sacral agenesis with iliolumbar articulation (type III) and a narrow pelvis [Figures 3a and 3b]. A magnetic resonance imaging (MRI) scan of the brain showed partial agenesis of the *corpus callosum* involving the anterior body, genu and rostrum. The T2 weighted image also showed an absence of the *septum pellucidum* along with partial lobar holoprosencephaly involving the posterior hemispheres [Figures 4a and 4b]. An MRI

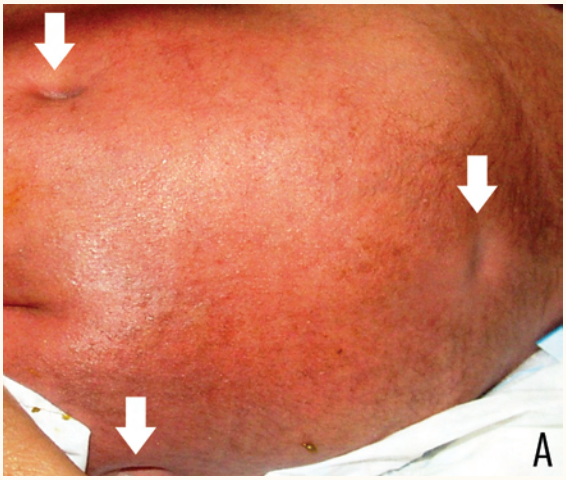

Figure 2a : Sacral dimples typical of caudal regression syndrome (block arrows)

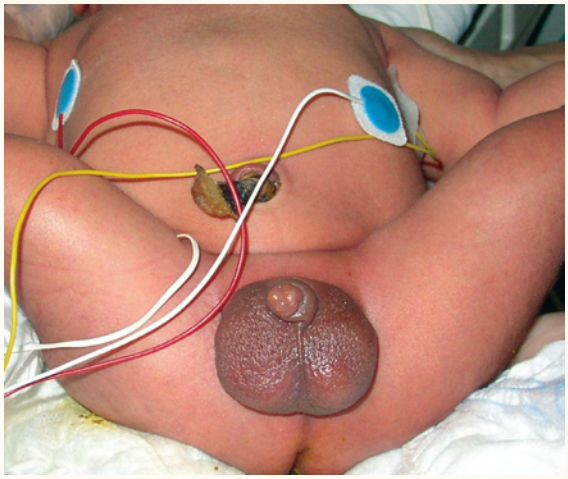

Figure 2b. V-shaped position of lower limbs and patulous anus

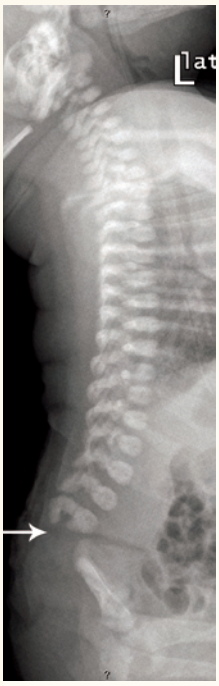

Figure 2a : X-ray showing sacral agenesis with iliolumbar articulation Type III

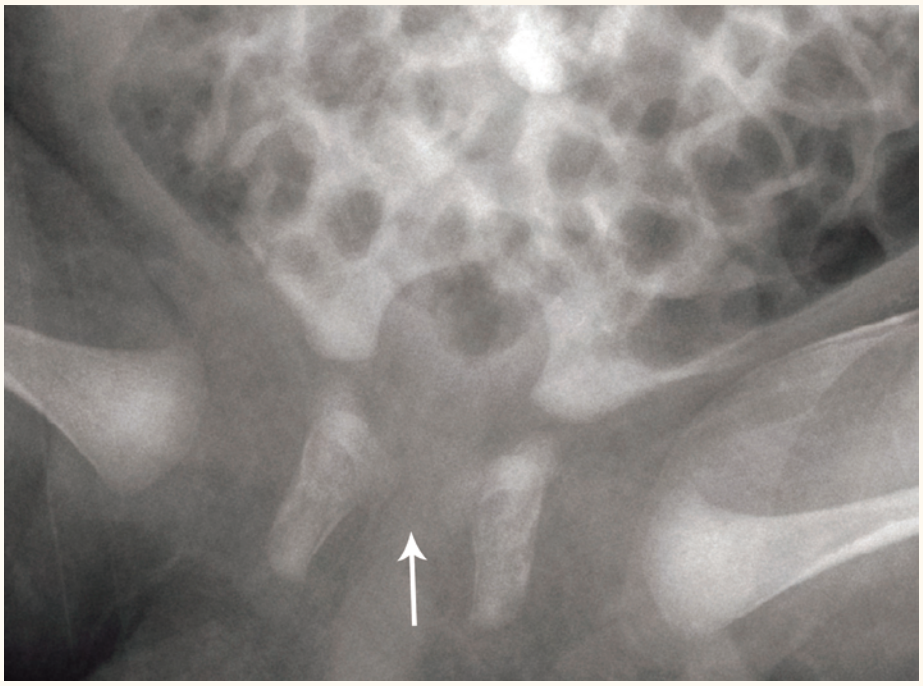

Figure 2b: X-ray showing narrow pelvis anterior posterior view

scan of the spine showed complete sacral agenesis, a tethered cord, and an intramedullary cyst in the lower part of spinal cord [Figure 5]. His abdominal ultrasound (US) and cardiac echocardiogram were normal. The orthopaedic follow-up showed a progressive enlargement of the intramedullary cyst which required excision at 6 months of age. The renal tract was normal with no infections or vesico-ureteric reflux until the time of this report, but the anus has remained patulous. His weight at 9 months follow-up was 10.1 kg and his head circumference 46 cm. Except for the effect of the lower limb anomaly the developmental milestones have been normal.

Discussion

Prospective and retrospective cohort studies have demonstrated an increased risk of congenital

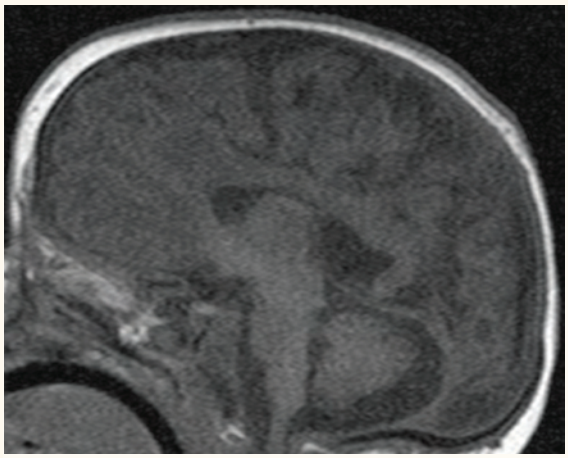

Figure 4a : Magnetic resonance imaging brain scan, sagittal view, showing anterior partial agenesis of corpus callosum

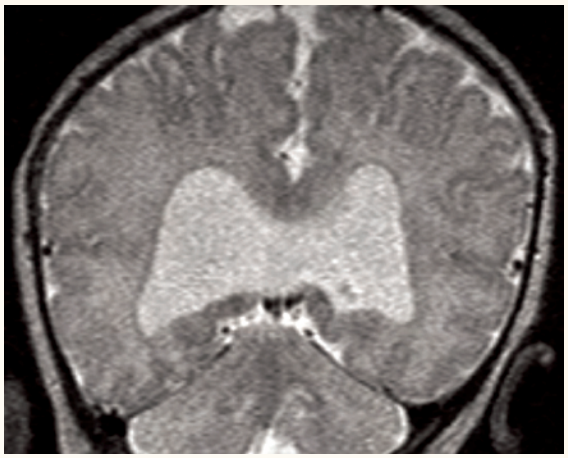

Figure 4b. Coronal view showing absence of septum pellucidum with partial lobar holoprosencephaly

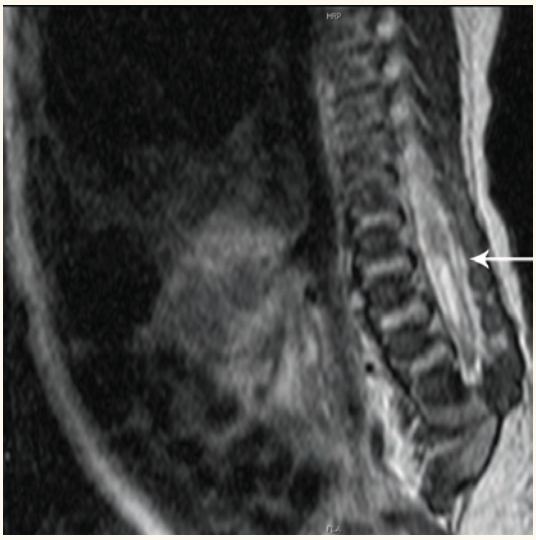

Figure 5: Magnetic resonance imaging scan of the spine showed complete sacral agenesis, tethered cord, and intramedullary cyst (arrow) in the lower part of spinal cord

abnormalities with pre-existing diabetes. Experimental studies suggest that hyperglycaemia is the major teratogen in diabetic pregnancies, but other diabetes-related factors may also affect fetal outcomes.[4] The teratogenic insult in diabetic embryopathy occurs between the third and seventh week of gestation at the initiation of organogenesis.[5] Miller *et al*.[6] found no major anomalies if the HbA1C was less than 6.9%, and significantly lower incidence if the HbA1C was less than 8.5% in the first trimester. Our patient had an HbA1C of 11.6% in the first trimester.

The main differential diagnosis of CRS would be sirenomelia. The relationship between CRS and sirenomelia is still debated with many researchers considering the latter to be a severe form of CRS.[7] The presence of renal and anal agenesis, fused lower limbs and a large single umbilical artery distinguish sirenomelia from CRS.

Maternal diabetes is associated with increased risk of other congenital central nervous system (CNS) malformations in the offspring. Holoprosencephaly (HPE) is a complex human brain malformation resulting from incomplete cleavage of the prosencephalon into right and left hemispheres, occurring between the 18th and the 28th day of gestation. The rostral neuropore closes at 24 days of gestation. Holoprosencephaly occurs due to rostral mesodermal dysfunction. At 74 days of gestation, axons cross through the dorsal region of the commissural plaque and start forming the *corpus callosum*. At 115 days of gestation, the *corpus callosum* reaches its adult form.[8] Many phenotypic variants of HPE exist with partial or complete agenesis of the *corpus callosum*.[9] Our patient had hyperglycaemia in the first trimester and this may explain the presence of both partial lobar HPE and partial agenesis of *corpus callosum*.

Some researchers have been successful in prenatal diagnosis in the first trimester based on a short crown rump length.[10] The crown rump length was reported to be normal in our patient at 10 weeks of gestation. On the 24 weeks scan, abrupt termination of the lumbar spine was noted.

In CRS, the mental functions are often normal and these children only need neurologic and orthopaedic support for the lower limbs and control of bowel and bladder. Morbidity and mortality is often due to a neurogenic bladder resulting in renal failure. Association of CRS with partial agenesis of the *corpus callosum* and partial lobar holoprosencephaly, as in our case, may result in additional neurological problems although at age 9 months this child appeared neurologically normal.

The incidence of all forms of diabetes is increasing among the Omani population. In a study in the Dhahira region of north-western Oman, 12.2% of stillbirths were among diabetic mothers.[11] Many Omani multigravida have several normal babies before developing pregestational and gestational diabetes. Because of a previous good obstetric history, they often come late in pregnancy for their first antenatal visit, thus losing out on an opportunity for early diagnosis of hyperglycaemia and anomalies.

Conclusion

Diabetes in pregnancy, whether insulin or non-insulin dependant, can be associated with multiple malformations in the fetus. Recognition of women with, and at risk of, diabetes is important as optimal glycaemic control in the periconceptional period may reduce the risk of embryopathy. In these mothers, early antenatal US may help in identifying this devastating disorder so that appropriate counselling can be offered.

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