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Case Report

Alobar holoprosencephaly, cebocephaly, and micropenis in a Klinefelter fetus of a diabetic mother

Chih-Ping Chen [a,b,c,d,e,f,g,*], Tsung-Hsien Su [a,h,i], Schu-Rern Chern [b], Jun-Wei Su [a,j], Chen-Chi Lee [a], Wayseen Wang [b,k]

[a] *Department of Obstetrics and Gynecology, Mackay Memorial Hospital, Taipei, Taiwan*
[b] *Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan*
[c] *Department of Medicine, Mackay Medical College, New Taipei City, Taiwan*
[d] *Department of Biotechnology, Asia University, Taichung, Taiwan*
[e] *School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung, Taiwan*
[f] *Institute of Clinical and Community Health Nursing, National Yang-Ming University, Taipei, Taiwan*
[g] *Department of Obstetrics and Gynecology, School of Medicine, National Yang-Ming University, Taipei, Taiwan*
[h] *Department of Nursing, Mackay Medicine, Nursing and Management College, Taipei, Taiwan*
[i] *Department of Obstetrics and Gynecology, Taipei Medical University, Taipei, Taiwan*
[j] *Department of Obstetrics and Gynecology, China Medical University Hospital, Taichung, Taiwan*
[k] *Department of Bioengineering, Tatung University, Taipei, Taiwan*

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Abstract

Objective: Coexistence of Klinefelter syndrome and holoprosencephaly (HPE) is rare. We report alobar HPE, cebocephaly, and micropenis in a Klinefelter fetus of a mother with type 2 diabetes mellitus with obesity and poor metabolic control.

Case Report: A 38-year-old woman was referred for therapy of type 2 diabetes mellitus with poor glycemic control at 24 weeks of gestation. On examination, she had a body height of 162 cm and a body weight of 105 kg. She had been treated with oral medication for diabetes mellitus for 4 years with poor maternal metabolic control. She had prominent glucosuria and glycemia. Her hemoglobin A1c was 7.5% (normal range: 3.4–6.1%), and the fasting glucose level was 141 mg/mL (normal range: 70–99 mg/mL) during this visit. Her husband was 46 years old. Prenatal ultrasound revealed a singleton fetus with fetal biometry equivalent to 24 weeks, alobar HPE, cebocephaly, and micropenis. As a result of poor maternal heath and fetal anomaly, the parents elected to terminate the pregnancy, and a 986-g male fetus was delivered with hypotelorism, HPE, cebocephaly, micropenis, and cryptorchidism. Cytogenetic analysis of the cord blood revealed a karyotype of 47,XXY. The parental karyotypes were normal. Polymorphic DNA analysis revealed a paternal origin of the extra X chromosome. Molecular analysis of the HPE genes of *SHH*, *ZIC2*, *SIX3*, and *TGIF* revealed no mutations.

Conclusion: Prenatal diagnosis of HPE should include a biochemical examination to identify metabolic factors such as maternal diabetes, and preventive management should be considered in subsequent pregnancies to achieve good control of maternal diabetes.
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Keywords: 47,XXY; holoprosencephaly; Klinefelter syndrome; maternal diabetes; prenatal diagnosis

Introduction

Klinefelter syndrome, or 47,XXY, is characterized by hypogenitalism and hypogonadism, with or without long legs, dull mentality, and/or behavioral problems, and is one of the most common causes of hypogonadism and male infertility, affecting 1 in 500 males [1]. Holoprosencephaly (HPE) is

* Corresponding author. Department of Obstetrics and Gynecology, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei, Taiwan.
E-mail address: cpc_mmh@yahoo.com (C.-P. Chen).

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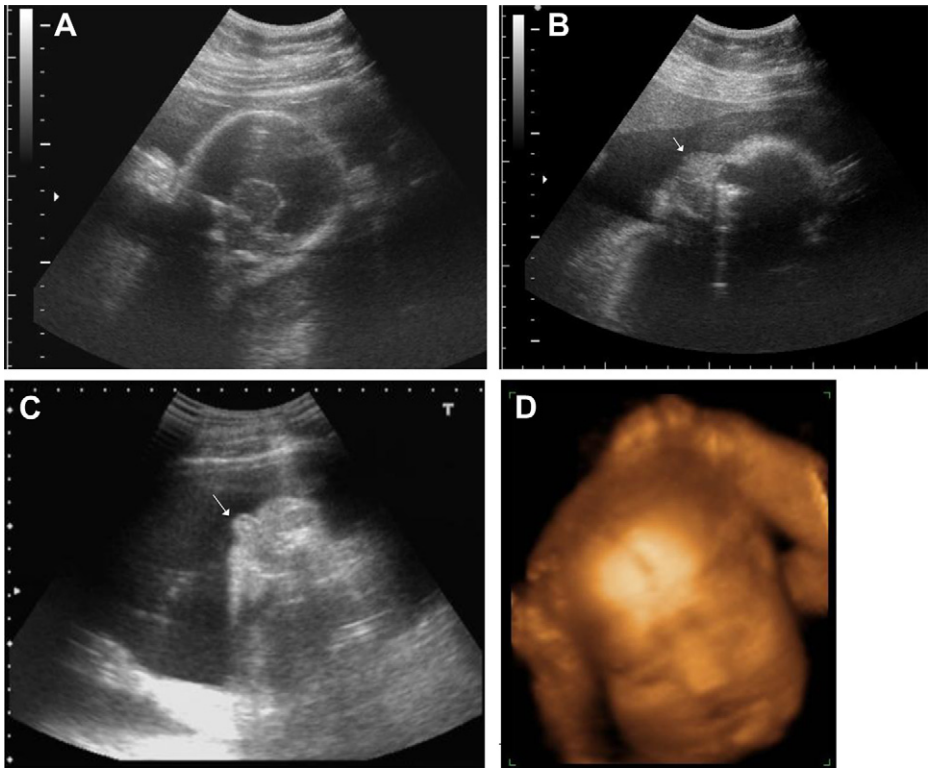

Fig. 1. Prenatal ultrasound at 24 weeks of gestation shows (A) alobar holoprosencephaly with a fused thalamus and a single ventricle; (B) a prominent nose (arrow); (C) micropenis (arrow); and (D) cebocephaly and hypotelorism on three-dimensional ultrasound.

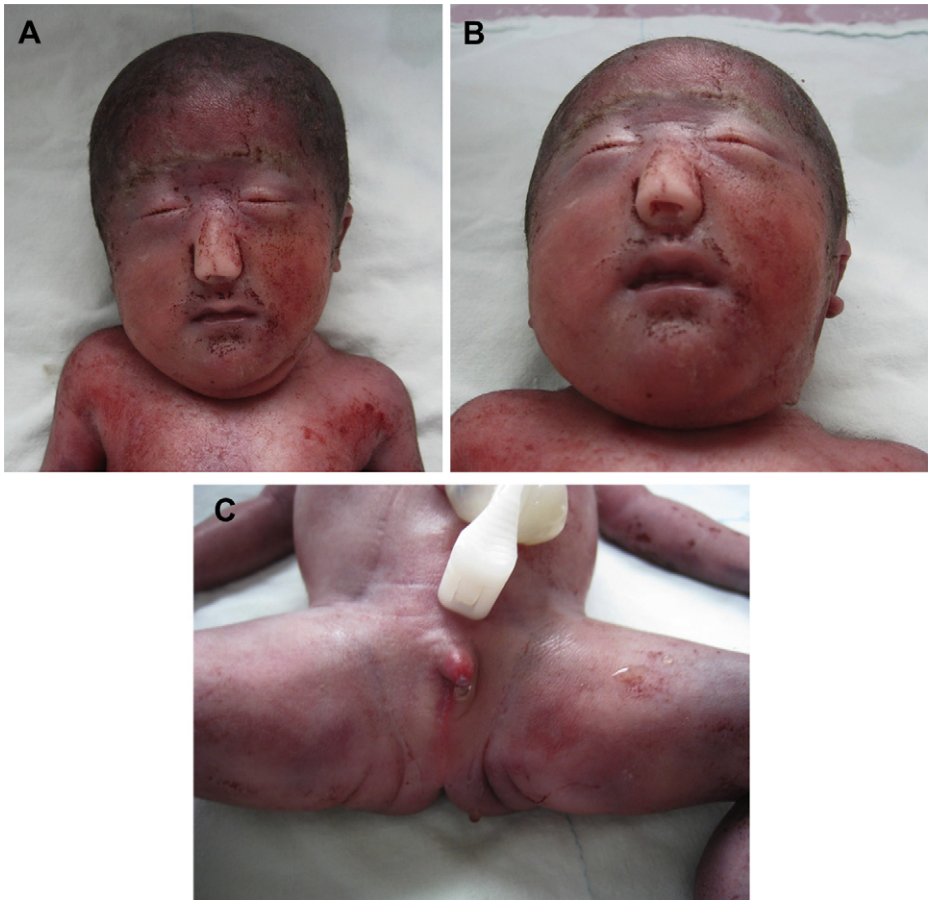

Fig. 2. The fetus at birth with (A) hypotelorism and cebocephaly; (B) a single nostril; and (C) micropenis and cryptorchidism.

a developmental anomaly that is characterized by impaired midline cleavage of the embryonic forebrain and comprises variable phenotypes including alobar HPE, semilobar HPE, lobar HPE, midline interhemispheric fusion variant, and microform, and affects one in 10,000 live births and four in 1000 conceptuses [2–6]. HPE can be caused by chromosomal abnormalities, microdeletions, or mutations in the HPE genes, genetic syndromes, and nongenetic risk factors such as maternal illness, therapeutic and nontherapeutic exposures, nutritional factors, sociodemographic factors and teratogens of maternal diabetes, hypocholesterolemia, alcohol, and retinoic acid [7–13]. Coexistence of Klinefelter syndrome and HPE is very rare. Here, we report the perinatal findings of alobar HPE, cebocephaly, and micropenis in a Klinefelter fetus of a mother with type 2 diabetes mellitus with obesity and poor metabolic control.

Case report

A 38-year-old, gravida 2, para 1 woman was referred for therapy of type 2 diabetes mellitus with poor glycemic control at 24 weeks of gestation. On examination, she had a body height of 162 cm and a body weight of 105 kg. She had been treated with oral medication for diabetes mellitus for 4 years, with poor maternal metabolic control. She had prominent glucosuria and glycemia. Her hemoglobin A1c was 7.5% (normal range: 3.4–6.1%), and fasting glucose level was 141 mg/mL (normal range: 70–99 mg/mL) during this visit. Her husband was 46 years old. The couple had a 1-year-old healthy son, and there was no family history of congenital malformations. Prenatal ultrasound revealed a singleton fetus with fetal biometry equivalent to 24 weeks, alobar HPE, cebocephaly, and micropenis (Fig. 1). The internal organs, limbs, and digits were normal. As a result of poor maternal heath and fetal anomaly, the parents elected to terminate the pregnancy, and a 986-g male fetus was delivered with hypotelorism, HPE, cebocephaly, micropenis, and cryptorchidism (Fig. 2). Cytogenetic analysis of the cord blood revealed a karyotype of 47,XXY (Fig. 3). The parental karyotypes were normal. Polymorphic DNA analysis revealed a paternal origin of the extra X chromosome (Fig. 4). Molecular analysis of the HPE genes of *SHH*, *ZIC2*, *SIX3*, and *TGIF* revealed no mutations.

Discussion

The present case represents a rare coexistence of two malformations: HPE and Klinefelter syndrome. To the best of our knowledge, only three cases with concomitant HPE and Klinefelter syndrome have been reported [14–16].

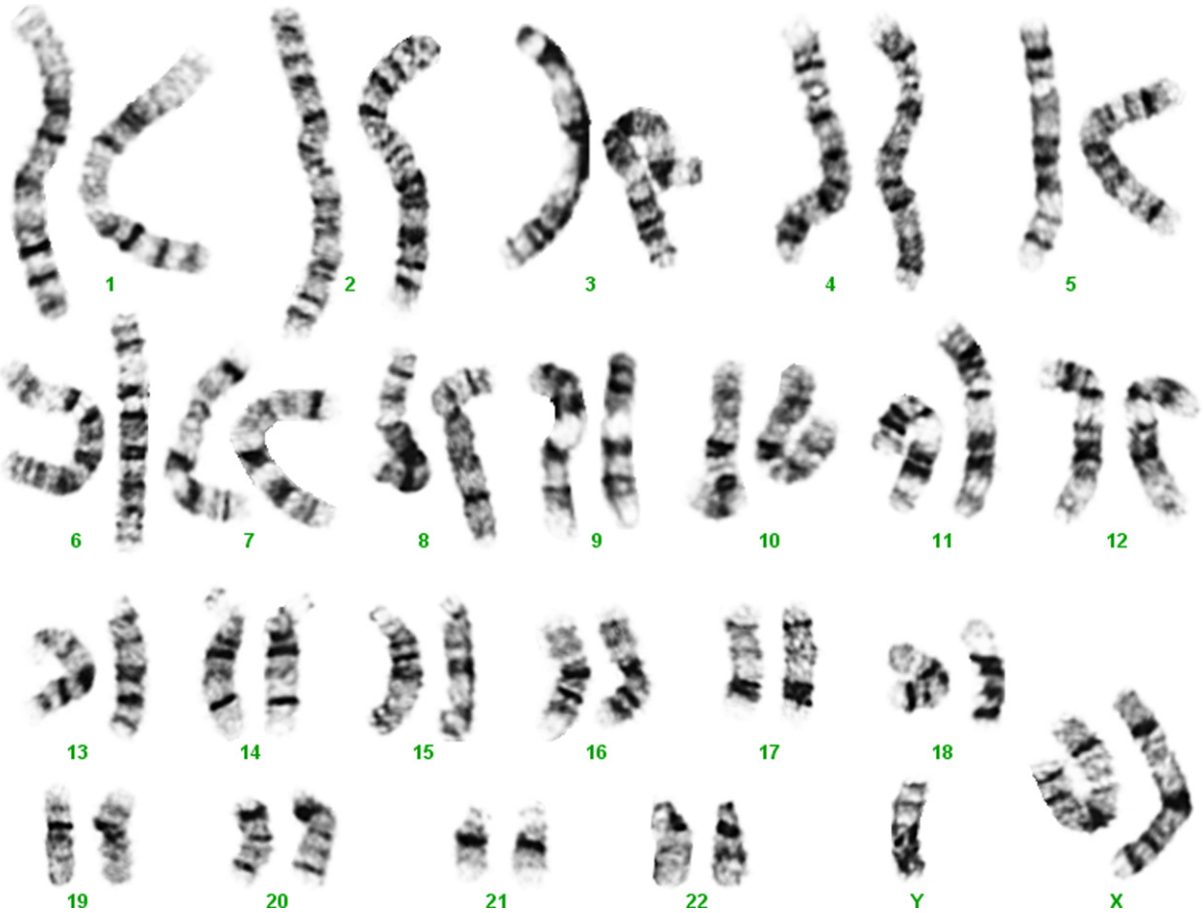

Fig. 3. A karyotype of 47,XXY.

Schnabel and Hansen [14] first reported a male neonate with a dysmorphic face, a nose with a single orifice, alobar HPE, and a karyotype of 47,XXY,18p−. The phenotype of HPE is likely to be caused by a deletion of 18p and haploinsufficiency of the *TGIF* gene. Armbruster-Moraes et al [15] reported first-trimester ultrasound diagnosis of premaxillary agenesis and HPE in a 27-year-old pregnant woman, and chorionic villus sampling revealed a karyotype of 47,XXY. Chen et al [16] reported a 2-day-old neonate with lissencephaly, HPE, microcephaly, hypotelorism, an upturned nose, cleft palate, Aicardi syndrome, and a karyotype of 47,XXY.

Studies on the extra X chromosome in Klinefelter syndrome have shown a frequency of 50% maternal origin and 50% paternal origin [17]. The present case was associated with advanced parental age and a paternal origin of aneuploidy. Klinefelter syndrome is known to be associated with double aneuploidy [18]. Major chromosomal abnormalities associated with HPE include trisomy 13, triploidy, trisomy 18, del(2p), del(2q), dup(3p), del(13q), del(18p), del(21q), and interstitial deletion of 14q13 [19]. 47,XXY is not a frequent aneuploidy associated with HPE, and HPE is not a characteristic feature of 47,XXY. The present case had characteristic Klinefelter syndrome features of hypogenitalia and hypogonadism, and manifested micropenis on prenatal ultrasound. Cytogenetic abnormalities have been reported in 32–41% of HPE patients, with trisomy 13 most common in up to 75%, triploidy in up to 20%, and trisomy 18 in up to 1–2% of the HPE cases with aneuploidies [13]. The present case was not associated with double aneuploidy, and there were no phenotypic features of trisomy 13, triploidy, or trisomy 18.

To date, at least 13 HPE loci and nine HPE genes have been identified [12]. About 22% of patients with HPE and normal karyotypes have mutations or microdeletions in one of the four most common HPE genes: *SHH* (OMIM 600725) at 7q36.3; *ZIC2* (OMIM 603073) at 13q32.3; *SIX3* (OMIM 603714) at 2p21; and *TGIF* (OMIM 602630) at 18p11.31 [12]. Other less frequent HPE genes include: *PTCH1* at 9q22.32 (OMIM 601309); *GLI2* (OMIM 165230) at 2q14.2; *DISP1* (OMIM 607502) at 1q41; *NODAL* (OMIM 601265) at 10q22.1; *FOXH1* (OMIM 603621) at 8q24.3; and *TDGF1* (OMIM 187395) at 3p21.31 [12]. The present case did not have mutations in the common HPE genes of *SHH*, *ZIC2*, *SIX3*, and *TGIF*.

The peculiar aspect of the present case was the association of HPE with elevated levels of maternal fasting glucose and glycosylated hemoglobin, and provides an example of major congenital anomalies during pregnancy in a mother with type 2 diabetes mellitus with obesity and poor metabolic control. Maternal diabetes is a well-recognized risk factor for HPE [20–22]. HPE is estimated to occur in 1–2% of births to diabetic mothers, indicating a 100–200-fold risk for HPE as

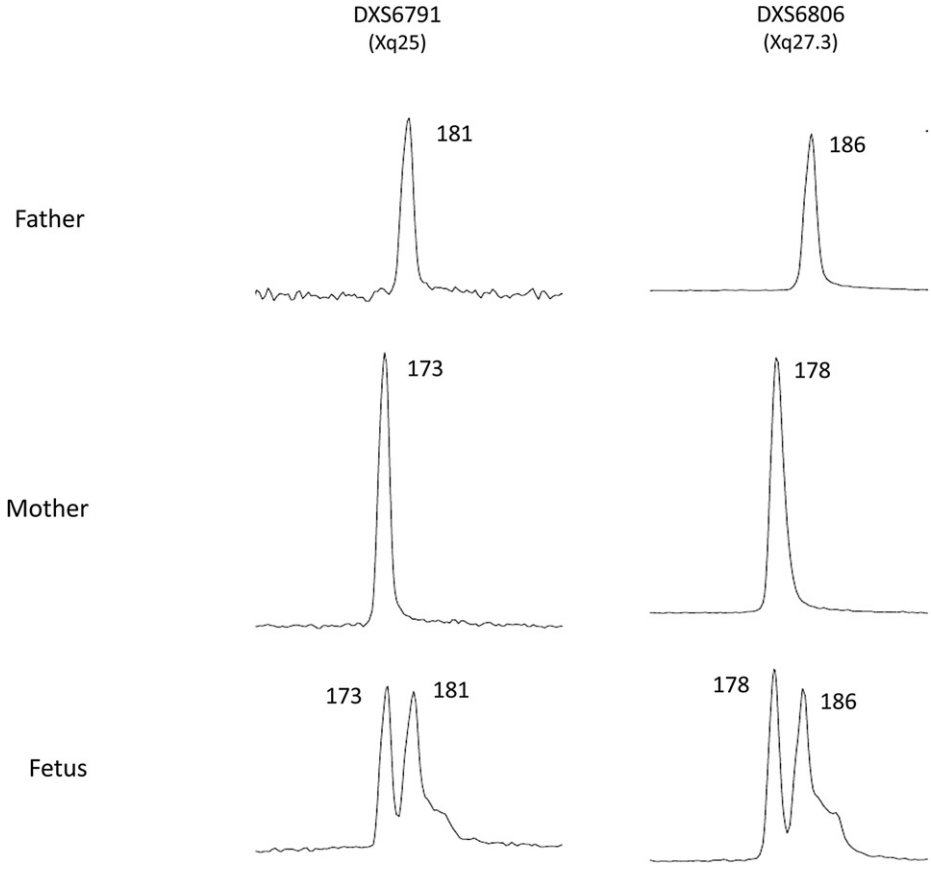

Fig. 4. Representative electrophoretograms of quantitative fluorescent polymerase chain reaction assays at short tandem repeat markers specific for chromosome X. The markers DXS6791 (Xq25) and DXS6806 (Xq27.3) show two different parental X alleles, indicating a paternal origin of the extra X chromosome in this case with 47,XXY.

compared to controls [23,24]. Pre-existing diabetes has been found in 6–9% of mothers of children with HPE [25,26]. In addition to HPE, diabetic embryopathy includes other structural abnormalities such as anencephaly, spina bifida, microcephaly, caudal regression syndrome, sacral agenesis, limb defects, renal agenesis, hydronephrosis, ureteric abnormalities, transposition of the great vessels, ventricular septal defect, atrial septal defect, coarctation of the aorta, cardiomyopathy, single umbilical artery, duodenal atresia, anorectal atresia, and small left colon syndrome [27]. Maternal diabetes has toxic effects on the embryos, and maternal obesity and diabetes are associated with an increased risk for central nervous system birth defects [28–31]. Prenatal diagnosis of HPE should include a biochemical examination to identify metabolic factors such as maternal diabetes, and preventive management should be considered in subsequent pregnancies to achieve good control of maternal diabetes.

Acknowledgments

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