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Environmental influence on predisposing genes for holoprosencephaly in monochorionic diamniotic twins

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Dear Editor,

Holoprosencephaly (HPE) is the most common structural anomaly of the developing forebrain characterized by incomplete separation of the prosencephalon. It is categorized into three main subtypes in order of decreasing severity: alobar, semilobar, and lobar. HPE encompasses a phenotypic spectrum that ranges from failure to partition the forebrain into hemispheres and cyclopia, to mild midfacial anomalies that occur without forebrain involvement. Clinical manifestations may include facial dysmorphic features, cognitive impairment, seizures, motor impairment, and ophthalmologic findings. Defects associated with HPE occur very early in embryonic development, at the stage of gastrulation. Incidence of HPE is 1:250 during embryogenesis [1], but it decreases to 1:16.000 among live deliveries due to the associated high rates of spontaneous abortion [2].

Case reports on HPE occurring in twins are few, even more rare in cases of monochorionic twins. Zhang *et al.* [3] described a singular case of discordant alobar HPE in monochorionic diamniotic twins with normal karyotype. The patient was a 21-year-old woman, gravida 1, para 0. At 24^{+6} weeks' gestation, severe brain malformations (alobar HPE, thalamus fusion, single brain tissue, hydrocephalus), cheiloschisis, and nose abnormality were detected in one twin by ultrasonography, while the other one was normal. Amniocentesis was performed to obtain amniotic fluid specimen of normal twin and karyotyping showed 46, XY. Patient denied any drug abuse, chronic disease, infections, and relevant familial or obstetric history. At 31 weeks' gestation polyhydramnios was found in the abnormal twin. Pregnancy was complicated with severe preeclampsia, intrahepatic cholestasis of pregnancy, and threatened premature labor. At 34^{+5} weeks' gestation, a cesarean section was performed. Malformed twin was a male weighing 2,829 grams and died immediately after birth. External examination revealed frontal bossing, hydrocephaly, hypotelorism of eyes, flat nasal bridge, macroglossia, and cheilo/palatoschisis. Karyotyping by G-banding of fetal umbilical blood specimen at birth in both twins verified 46, XY. Autopsy was not performed because of the lack of parental consent. The authors did not suggest a possible cause responsible for this singular case report. Indeed, the etiology of HPE is heterogeneous and still incompletely understood. It involves a complex interplay between various environmental factors, syndromic disorders, chromosomal anomalies, and heterozygous variants in several HPE-associated genes [1]. In non-syndromic HPE (30-40%) heterozygous mutations or small copy number variation of few genes (SHH, MIM 600725, SIX3, MIM 603714, ZIC2, MIM 603073, and TGIF, MIM 602630) are found in approximately 30% of cases, while mutations in any of over ten additional genes are detected with a much less frequency [4]. In literature, variable expressivity or incomplete penetrance have been reported in multiple cohorts, suggesting a complex inheritance [5]. Studies on gene-environment interactions in mice have supported this scenario of complex inheritance in HPE [6]. In fact, Capobianco *et al.* [7] highlighted the teratogenic effect of hyperglycemia, hyperinsulinemia, and insulin-resistance (IR), describing a case of alobar HPE and trisomy 13 with maternal gestational diabetes mellitus (GDM) in dietary treatment.

GDM is defined as any degree of glucose intolerance with an onset or first recognition during pregnancy. It is a common complication of pregnancy, associated with a high incidence of hypertensive disorders, like gestational hypertension, preeclampsia, and eclampsia, and an increase risk of excessive fetal growth, polyhydramnios, and preterm labor. Physiological pregnancy is characterized by elevated levels of hormones and other proteins having insulin-antagonistic effects, that increase IR in peripheral tissues, inducing compensatory hyperinsulinemia. Therefore, pregnancy can unmask GDM in preexisting conditions associated with IR, like obesity, prediabetes, or polycystic ovary syndrome (PCOS).

PCOS is recognized as the most common endocrine-metabolic disorder of reproductive-aged women, characterized by oligo-anovulation, polycystic ovaries, clinical/ biochemical

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hyperandrogenism, and often associated with IR even in normoweight women [8, 9]. PCOS patients have also multiple risk factors that may lead to several complications during pregnancy, as for example obesity, impaired glucose tolerance or diabetes, thyroid disorders, pro-oxidative status, relative hyperaldosteronism, and hypertension [10]. Indeed, the prevalence of GDM, preeclampsia, premature delivery, and caesarean section and other cardiovascular events during pregnancy is significantly increased in PCOS patients compared with healthy women [11].

In pregnancy liver induction of lower sex hormone binding proteins reduce bioavailability of androgens; however, this decrease is impaired in pregnant PCOS women. Controversial data are available concerning the pathophysiological effects of hyperandrogenism on the development of complications during pregnancy. Some studies showed that women, who were more hyperandrogenic and more insulin resistant during pregnancy, had a worse pregnancy outcome compared with those showing lower degree of hyperandrogenism and IR [12]. Some authors reported increased androgen concentrations in women with high blood pressure and preeclampsia, suggesting a certain pathological role of androgens in the hemodynamic changes responsible for the preeclampsia development [13, 14].

In the singular case of discordant alobar HPE in monochorionic diamniotic twins with normal karyotype presented by Zhang *et al.* [3], we can hypothesize the presence of some genetic defects partially unmask by maternal condition. Monozygotic twins originate from a single zygote, and share the same genetic material and similar intrauterine environment. It is well known that mutation carriers display highly variable clinical presentation, because the penetrance and expressivity of a predisposing mutation is graded by genetic or environmental modifiers. A forthright GDM could have caused the development of the syndrome in both twins. Instead, PCOS, IR, and an undiagnosed mild hyperglycemia could have led to a hostile intrauterine environment and only one fetus could have developed the disease due to different penetration of HPE.

Cosmi *et al.* [15] previously evaluated dimensions and volume of yolk sac in pregnancies complicated by diabetes using two- and three-dimensional sonography and they observed a faster growth and a more precocious involution of the yolk in diabetic pregnancies. The authors speculated that the alteration in the speed of growth of the structure could be correlated to the diabetic environment. It could be interesting to evaluate if this finding is present even in women with hyperinsulinemia and IR, and if it this could be used as a marker of hostile intrauterine environment. Further studies are needed to better understand the function of additional genes and gene-environment interactions. With the development of next-generation sequencing, more and more potential genetic causes will be discovered to explore the discordant abnormalities in monozygotic twins.

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