Fetal malformations and fetal death in a case of parental thrombophilia

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Case report

B.T., a 26 year old pregnant woman who reached 41 weeks of gestation (gravida 1, para 0), came to our observation in June 1994, for a spontaneous onset of labour. She was taken care of elsewhere during pregnancy. The course of gestation had been normal and no risk factor was evident from both the clinical history and the analysis of the patient’s clinical condition. Laboratory tests were normal. Previous ultrasound scans revealed a fetal growth at the lower end of the normal range expected for gestational age, but Doppler studies showed that the fetus was healthy. The patient’s body weight was 64 kg (increased 10 kg during pregnancy) and blood pressure was 110/70 mmHg. After an uneventful labour, a female baby weighing 2600 g, with Apgar scores of 8/9, was delivered vaginally. However, the infant presented at birth a left dorsolumbar hemispondylia and an oesophageal atresia type III. None of these anomalies had been diagnosed prenatally through a serial sonographic follow-up. The neonatal karyotype was 46, XX. The infant underwent surgery repeatedly for correction of the oesophageal atresia and the hemispondylia. No correction of spina bifida occulta was considered necessary at that stage, given its entity and the absence of clinical neurological deficits. Currently the child is fourteen years old. A mild and transient gastro-oesophageal reflux, besides a 30° kyphosis and 25° scoliosis of the dorsolumbar tract of the rachis requiring physiotherapy, persist. Nevertheless, the child does not show any mental nor neurological deficits.

In 2001, the woman, at 33 years of age, became pregnant again; however, fetal death occurred at 20 weeks’ gestation. No fetal malformations were revealed by the autopsy; however, the placenta showed largely extended infarctions. Since the woman desired a further pregnancy, both parents underwent screening for thrombophilias. Eterozygosity for both the C677T and the A1298C mutation in the methylene tetrahydrofolate reductase (MTHFR) gene, as well as for the Factor V Leiden mutation (G1691A) were found in the woman. Eterozygosity for the C677T MTHFR gene mutation was also demonstrated in the husband. A screening for thrombophilias was therefore advised to be carried out in the live infant as well, which brought to the identification of etezygosity for the Factor V Leiden mutation and homozygosity for the C677T MTHFR gene mutation.

In 2003, the woman, (gravida 3, para 1), came to us again for obstetric care. Early therapy with low molecular weight heparin (enoxaparin) was carried out at a dose of 4000 units/day, in addition to treatment with folic acid and vitamins B6 and B12. The course of this pregnancy was uneventful. Blood coagulation tests, as well as the levels of Antithrombin III, Protein C, Protein S and homocysteine kept within normal ranges throughout the pregnancy. Screening for thrombophilias through amniocentesis revealed etezygosity for the C677T MTHFR gene mutation. The prenatal ultrasound follow-up showed normal fetal growth and absence of anomalies. Doppler studies showed normal velocimetry patterns. A caesarean section was performed due to fetal face presentation at 39 weeks’ gestation, and a healthy male baby weighing 3050g, with Apgar scores 9/10, was delivered.

Discussion

Before 1993, known inherited thrombophilias included deficiencies of protein C, protein S and antithrombin; however, taken together, such defects are responsible for only 15% of familial thrombophilias, and less than 5% of all venous thromboses (1). Thus, the possibility of finding a relationship between thrombophilia and obstet-
ric pathologies was remarkably low. More recently, novel genetic thrombophilias have been identified. The resistance to the anticoagulant activity of activated Protein C (APC), accounting for up to 40% of all thromboses, is due to Factor V Leiden mutation in 95% of cases (2); the estimated carrier frequency of this mutation is about 5% in the Caucasian population (European, Jews, Israeli Arabs, Indians) (3) reaching to about 10-15% in some European countries (4). Hyperhomocysteinemia resulting from the C677T mutation in the MTHFR gene is known since the sixties as a risk factor for vascular damage (5), but only recently it has been implicated in obstetric complications (6): homozygosity for this mutation is reported in about 12% of the white population (7). The G20210A mutation in the factor II (prothrombin) gene is another cause of thrombophilia: heterozygosity for such mutation is reported in 2-3% of the white European population (8).

Thus, recent studies have demonstrated an increasing role of genetic and acquired thrombophilias in the pathogenesis of several serious obstetric pathologies, such as deep venous thrombosis in pregnancy, preclampsia, spontaneous miscarriage, late fetal loss, abruptio placentae and other placental lesions (placental infarctions) and intrauterine growth retardation (6, 9, 10). Hyperhomocysteinemia has also been associated with an increased incidence of neural tube defects (NTD), which is related to impaired function of methionine synthetase, an enzyme involved in myelin synthesis (11).

Even more recently it has been suggested that thrombophilias represent risk factors for those fetal malformations, whose pathogenesis is potentially related to a vascular thrombotic or ischemic event. The C677T mutation in the MTHFR gene has been found to be associated with terminal limb defects (12). It has also been suggested that Factor V Leiden, increased lipoprotein (a), protein C and protein S deficiency exert a role in the pathogenesis of congenital porencephaly (13). Association of the Leiden mutation with congenital microcephaly has also been reported (14). A high prevalence of factor V Leiden and the R353Q factor VII polymorphism has been found in patients with intestinal atresia (15). Interestingly, the latter study failed to demonstrate thrombophilias in some patients, suggesting a multifactorial etiology for such pathology (15).

Only a few studies have investigated the role of fetal thrombophilia in the pathogenesis of the above mentioned obstetric pathologies, although it must be reminded that some thrombophilic mutations are inherited in an autosomal dominant fashion and, therefore, may be potentially inherited also by the father: i.e., a fetus may carry a thrombophilia, even if the maternal screening is negative. One study has shown that early spontaneous miscarriage and placental infarction are significantly associated with a fetal rather than a maternal thrombophilia: interestingly, infarctions were detected in the distribution of the fetal vessels coursing along the fetal side of the placenta (16). We may reasonably speculate that many more obstetric pathologies may be related to fetal thrombophilias. Similarly, some fetal malformations might be correlated to a fetal rather than a maternal thrombophilia. Relevant to this, an investigation has demonstrated a significant association between the fetal, but not the parental, C677T mutation in the MTHFR gene with the risk of NTD (17).

In our case, the first daughter of the couple carried a double thrombophilia, one of which was due to the homozygosity for the C677T MTHFR gene mutation: the thrombogenic and teratogenic (regarding NTD) risk was therefore higher than expected on the basis of just the maternal genotype. She suffered from hemispodylia and spina bifida occulta, as described above. Oesophageal atresia was also observed in this patient.

In the study by Johnson and Meyers investigating the prevalence of fetal thrombophilias in cases of intestinal atresia (2001) (15), oesophageal atresia was not includ-
ed among the investigated malformations, since its pathogenesis is postulated to be different from ischemic insult. Our case does not demonstrate a causal relationship between fetal thrombophilia and oesophageal atresia, but encourages new investigations to be carried out in order to evaluate a possible association between the two factors.

Moreover, this case report suggests the question of whether, in the case of a maternal thrombophilia, the father should also be screened for thrombophilia, and whether, if the screening is positive, an early maternal therapy should be administered. In fact, although there is no definitive evidence indicating the possibility of improving the outcome of subsequent pregnancies, preliminary studies suggest a favourable effect of low molecular weight heparin on the pregnancy outcome of women with thrombophilia and with a history of obstetric complications (18). Moreover, there are no contraindications regarding the use of folic acid and vitamins B₆ and B₁₂ before and throughout the pregnancy, whereas their positive effect has been reported (9).

In our case, the third pregnancy of the couple, during which early therapy with enoxaparin, folic acid, vitamins B₆ and B₁₂ was carried out, was uneventful and the infant is currently healthy; however, the infant was only heterozygous for the C677T MTHFR gene mutation. Nevertheless, although an firm conclusion on this issue may not be drawn, the report suggests that the above described therapy is effective in preventing complications potentially related to parental and fetal thrombophilias.

References