To the editor:

HFE mutations in the pathobiology of hemophilic arthropathy

A recent paper by Hakobyan et al1 in Blood has demonstrated that iron stimulates synovial cell division through oncogene (mdm2) activation in models of hemophilic arthropathy. This paper was the topic of an Inside Blood comment by Abshire,2 who stated that it would be important to identify other genetic factors explaining the heterogeneity of hemophilic arthropathy. In this letter we present relevant results of the severity of arthropathy associated with mutations in the HFE gene, namely C282Y and H63D, in 34 hemophilia patients. The results indicate that severity of the arthropathy measured both by number of hemarthrosis per year and number of affected joints is associated with the presence of the mutations, particularly with C282Y. Mechanisms may involve abnormal circulating iron levels in C282Y carriers and/or an increased efflux of iron from macrophages in affected joints.

Wen et al3 and Hakobyan et al1 have recently identified changes in oncogene expression in models of hemophilic arthropathy as the possible molecular basis of the effect of iron on synovial cell division originally described by Nishiyama4 in rheumatoid arthritis patients. In an Inside Blood, the need to look for additional genetic factors contributing to the establishment of hemophilic arthropathy was discussed.2

We recently concluded a pilot study of the frequency of HFE mutations in a group of 34 hemophilia patients aged between 20 and 71 years, diagnosed before 1985 and followed up in Santo António General Hospital in Porto. The study design was approved by the Hospital Ethical Committee. Informed consent was provided according to the Declaration of Helsinki. All patients were genotyped for C282Y and H63D mutation as described.5 Allele frequencies of the C282Y (6 heterozygous and 2 compound heterozygous for C282Y and H63D) and H63D (12 heterozygous and 1 homozygous) mutations in this group of patients were 0.118 and 0.235, respectively, as opposed to the reported allele frequencies in Porto patients of 0.032 for the C282Y, 0.235, respectively, as opposed to the reported allele frequencies in Porto patients.6

The patients were grouped according to severity of disease: severely affected (n = 17; factor VIII [FVIII]/IX ≤ 1%), moderately affected (n = 11; FVIII/IX > 1% and ≤ 5%), and mildly affected (n = 6; FVIII/IX > 5%). Arthropathy severity was arbitrarily defined as number of hemarthrosis/year and number of affected joints. No differences were seen between the ages of the patients in the 3 groups. The results are summarized in Figure 1.

Analysis of the impact of the HFE mutations on the number of hemarthrosis/year showed that 5 (63%) of 8 HFE-mutated patients in the severe group had more than 6 episodes in contrast with 1 (14%) of 7 wild-type patients (Figure 1A). In terms of number of affected joints, 100% (8/8) of HFE-mutated patients in the severe group had more than 3 joints affected as opposed to 4 (57%) of 7 wild-type patients (Figure 1B). The impact of HFE mutations was particularly visible in the moderate group where C282Y carriers are segregated from the other genotypes (Figure 1B). All C282Y carriers (n = 3) had more than 3 affected joints in contrast to the H63D single carriers or wild-type patients. The only compound heterozygous (in the moderate group) had the most severe signs of arthropathy in this group (Figure 1A-B). These results point to an impact of HFE mutations in hemophilic arthropathy compatible with a deleterious systemic effect of iron associated with deregulated iron absorption.

The results echo the results of an earlier study of the activation of the rat synovium by iron where a peak of the mitotic activity was seen among synovial cells at 8 hours after one single injection of ferric citrate sufficient to cause a transient increase above 100% in transferrin saturation.6 In conclusion, gene mutations that influence circulating iron levels and that in addition increase iron exit from macrophages7 should be considered among the genetic factors contributing to the heterogeneity of hemophilic arthropathy, as put forward by Abshire.2

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References


To the editor:

Use of desmopressin (DDAVP) during early pregnancy in factor VIII–deficient women

Desmopressin (DDAVP) is being used with caution in the first 2 trimesters of pregnancy in women with bleeding disorders1,2 because there is concern that the compound may cause placental insufficiency due to arterial vasoconstriction and increase the risks of miscarriage due to an oxytocic effect and to maternal and/or neonatal hyponatremia.3 The latter concern is in principle justified because desmopressin is a potent antidiuretic nonapeptide that acts thorough V2 vasopressin receptors.4 On the other hand, its potential for vasoconstriction and uterus contraction is negligible because the compound is practically devoid of these biologic activities related to the activation of V1 vasopressin receptors.5 Evidence of its safety during pregnancy in women with diabetes insipidus is available.5 Since the original description of its use for the treatment of mild hemophilia and von Willebrand disease (VWD),5 between 1988 and 2002 we used desmopressin in 32 pregnant women with low factor VIII levels in order to improve hemostasis at the time of invasive procedures.

Of 32 pregnant women, 27 were obligatory carriers of hemophilia with factor VIII deficiency, presumably due to extreme random inactivation of their normal X chromosome (lyonization), and 5 had type 1 VWD. Twenty women underwent chorionic villus sampling at gestational weeks 11 to 12 for prenatal diagnosis of hemophilia, the remaining 12 underwent amniocentesis at weeks 16 to 18 for prenatal diagnosis (7 hemophilia carriers) or karyotyping (5 women with type 1 VWD). In all women, factor VIII levels were low enough to engender an increased risk of bleeding (median, 60 U/dL; range, 40-121 U/dL). In all 32 women there was no abnormal bleeding and in 20 of them pregnancies went successfully to term with the delivery of healthy newborns. In the remaining 12 cases, male fetuses affected by hemophilia on genotyping were aborted under coverage with additional doses of desmopressin. There was no side effect in the treated women other than mild facial flushing and headache and no significant increase in body weight.

This series shows that desmopressin can be used during the first and second trimester of pregnancy and that it is safe during invasive procedures that increase per se the risk of miscarriage. Electrolytes and osmolality were not measured because this is our routine protocol. However, there was no clinical sign of water intoxication or body weight increase in these women, who were warned to restrict fluid intake.

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References


To the editor:

Hyperhomocysteinemia: cause or effect of disease?

We read with interest the article on the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism by Frederiksen et al.1 We do not agree with the hypothesis of the authors that testing C677T MTHFR is an alternative approach to establish if hyperhomocysteinemia is a cause or simply an effect of the disease. Indeed, hyperhomocysteinemia is not a monogenic condition, but a number of acquired and inherited risk factors contribute to its development. Several polymorphisms in the
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