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Respiratory burst activity in late pregnancy in a carrier of X-linked chronic granulomatous disease

Screening for chronic granulomatous disease (CGD) and carrier status is carried out by the nitroblue tetrazolim test. The diagnosis is confirmed by quantitative tests of respiratory burst activity. Production of reactive oxygen intermediates may be increased in late pregnancy which may compensate for the otherwise low level in a CGD carrier, thus confounding diagnosis for the unwary clinician.

Sir,

We recently diagnosed chronic granulomatous disease (CGD) in a 6-year old boy who had a long history of recurrent bacterial and fungal infections involving the lung, liver and kidney. Diagnosis was made by counting nitroblue-tetrazolium (NBT)-reducing phagocytes (NBT slide test)[1] as well as by evaluating the oxidative burst activity by means of both SOD inhibitable Cytochrome c reduction (Cyt. c red.)[2] and flow cytometric (DCF fluorescence)[3] assays. To investigate the possibility of X-linked transmission we tested both his parents by means of the NBT slide test which revealed that ~70% of maternal neutrophils at 38 weeks of an uneventful gestation did not produce reactive oxygen intermediates after stimulation with either N-formyl-methionyl-leucyl-phenylalanine or phorbol myristate acetate. However, at the same stage of gestation, when the maternal neutrophils were analyzed by means of both Cyt. c red. and DCF fluorescence assays, no significant changes in the fMLP- or PMA-induced oxidative burst activity occurred compared to the changes found in a group of thirty randomly selected normal non-pregnant subjects. Repeat testing of the maternal neutrophils was performed five months after delivery of an apparently healthy female. Unanimously abnormal results obtained by the three tests were consistent with the diagnosis of carrier status. While the NBT-slide continued to show the same percentage of NBT-negative neutrophils, the amount of oxidative burst activity was 50 percent less than that recorded for neutrophils from control subjects (Table 1; Figure 1).

Although X-linked CGD carriers are usually healthy (as was our female case), with no manifestations of CGD, there are reports of a higher incidence of

Table 1. NBT slide test. Percentage of NBT non-responding cells.

Subjects	*Healthy donors*	*CGD-affected subjects*	*CGD carrier during pregnancy*	*CGD carrier 5 months after pregnancy*
% NBT non-responding cells	0-2	98-100	70-67	71-67

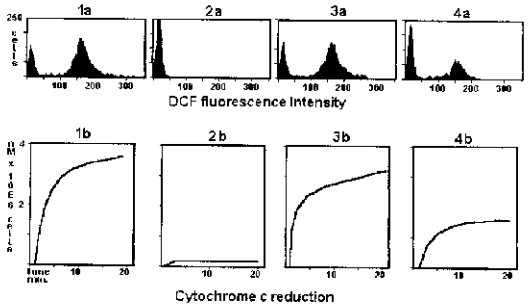

Figure 1. Evaluation of oxidative burst activity performed by flow cytometric assay (DCF fluorescence, and SOD inhibitable Cytochrome c reduction.

autoimmune disease and mouth ulcers in carriers.[4,5] Yet, a very recent report describes the occurrence of retinal lesions in patients as well as in carriers.[6] Thus a reliable screening of carriers of CGD may give us a better understanding of the natural history of non-infective manifestations of CGD and potentially provide new insights into the clinical spectrum of CGD, its pathogenesis and ways to treat it.

The diagnosis of CGD and carrier status routinely relies upon the demonstration of an absent or greatly diminished neutrophil respiratory burst. For initial screening,the NBT slide test is rapid and relatively simple. For confirmation, a quantitative test of the respiratory burst is deemed necessary.[7] Identification of the specific genetic subgroup for a patient is required for purposes of genetic counselling and prenatal diagnosis. Although this report of one case provides only limited information, it suggests that quantitative tests might fail to detect X-linked CGD carriers in late pregnancy. Production of reactive oxygen intermediates has been reported to be higher in pregnant women during the peripartal period than in early pregnancy or in non-pregnant women.[8,9] Accordingly, it is possible that an apparently normal oxidative burst activity might have been achieved in our 38-week pregnant carrier by enhanced activity of the normal population of cells. At any rate,whatever the mechanism(s) accounting for the present findings, we hope the information given here will alert the readers to the reliability of neutrophil function screening tests in identifying maternal CGD carrier status in pregnancy. These issues need to be investigated further in women throughout their pregnancies.

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Key words

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Factor V Leiden in absence of activated protein C resistance after orthotopic liver transplantation in a patient without thrombosis but with familial thrombophilia

There are reports that orthotopic liver transplantation may produce phenotypic correction of activated protein C (APC) resistance in patients with FV Leiden. We report the case of a factor V Leiden heterozygote with absence of APC reistance following an orthotopic liver transplantation. The patient suffered not thrombotic episodes prior to or after the transplant despite a strong history of familial thrombophilia.

Sir,

We report a heterozygous FV Leiden individual with absence of activated protein C (APC) resistance following orthotopic liver transplantation. APC resistance is associated with a mutation in factor V gene, named FV Leiden.[1,2] APC resistance is defined as a poor anticoagulant response of the patient's plasma to APC. Some patients with APC resistance do not have the FV Leiden, and this suggests the existence of an acquired APC resistance phenotype.[3] However, the existence of the FV mutation without APC resistance is a rare cause of discrepancy between the genotypic and phenotypic analyses.[4,5]

The propositus (II-5) (Figure 1) is a 48-year old man with a family history of thrombosis but with no personal history of deep venous thrombosis (DVT). He underwent orthotopic liver transplantation in 1994 because of alcoholic cirrhosis. Figure 1 shows the pedigree of the family. The father of the propositus (I-1) died at the age of 55 probably as a result of cerebral thrombosis. The mother of the propositus (I-2), aged 77, developed cerebrovascular ischemia at the age of 73. The propositus's sister (II-3) had a DVT at 29 in puerperium and one of his brothers (II-8) had a DVT and pulmonary embolism at the age of 37