Una bambina con Diabete Mellito tipo 1 e la madre con 13 episodi di TIA ?!

Caserta, **15 settembre 2012**

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Paziente: Federica D.
Data di nascita: 17/04/1997.
Diabete Mellito tipo 1 (ICA tracce, GAD >100 UA , IA2 > 4,6 UA)
esordito ad ottobre 2006 all'età di 9 a e 6/12.

Dati di rilievo dell'anamnesi familiare :
Primogenita da genitori non consanguinei.
Madre : 11 episodi di TIA (?!) , il primo dei quali insorto all'età di 23 anni

Madre e Nonna materna entrambe portatrici della mutazione C677T del MTHFR, in omozigosi.

Per la storia clinica della madre (apparenti episodi tromboembolici ricorrenti in età giovanile) si eseguivano, nella paziente, i seguenti esami:

PT: 11 sec (v.n. 10-12 sec)

PTT: 32 sec (v.n. 26-37)

ATIII: 106 % (v.n. 77-132 %)

fibrinogeno 580 ng/dL (v.n. 150-400).

Proteina C: 84 % (v.n. 55-111%)

Proteina S: 87% (v.n. 70-140)

Omocisteina: 27 mcmol/L (v.n. 6-12)

Resistenza alla proteina C attivata: 4 Ratio (v.n. >1,8)

Lupus anticoagulanti: negativo

Anticorpi anticardiolipina: 6,1 U/mL (v.n. 0-20)

Anticorpi antifosfolipidi IgG: 3 U/mL (v.n. 0-11)

Anticorpi antifosfolipidi IgM: 4 U/mL (v.n. 0-11)

Analisi genotipiche

- **Mutazione C677T del MTHFR: Positiva (omozigote, genotipo T/T)**
- Mutazione A1298C del MTHFR: Negativa
- Polimorfismo Leiden del Fattore V: G1691/G1691 (wild type)
- Polimorfismo HR2 del Fattore V: H1299/H1299 (wild type)
- Polimorfismo G20210A del gene della Protrombina: G20210/G20210 (wild type)
- **Polimorfismo 455G/A del Beta-Fibrinogeno: 455A/455G (eterozigote)***: la presenza dell'allele 455A del Beta-fibrinogeno, è associata, anche in eterozigosi, a livelli plasmatici elevati di fibrinogeno che predispongono a fenomeni di trombosi venosa.*
- Polimorfismo dell'Apolipoproteina B (APO B): assenza delle mutazioni C9774T e G9775A del gene dell'APO B
- Polimorfismo dell'Apolipoproteina E: **mutazione C3932T** (Arg 112 Cys) allo stato **eterozigote**
- Polimorfismo dell'enzima di Conversione dell'Angiotensina (ACE): **polimorfismo allo stato eterozigote** (inserzione/delezione).

N Engl J Med. 2006 Apr 13;354(15):1578-88. Epub 2006 Mar 12.

Homocysteine lowering and cardiovascular events after acute myocardial infarction.

Bønaa KH, Njølstad I, Ueland PM, Schirmer H, Tverdal A, Steigen T, Wang H, Nordrehaug JE, Arnesen E, Rasmussen K; NORVIT Trial Investigators.
Institute of Community Medicine, University of Tromsø, Tromsø, Norway. kaare.bonaa@stolav.no

METHODS: The trial included 3749 men and women who had had an acute myocardial infarction within seven days before randomization. Patients were randomly assigned, in a two-by-two factorial design, to receive one of the following four daily treatments: 0.8 mg of folic acid, 0.4 mg of vitamin B12, and 40 mg of vitamin B6; 0.8 mg of folic acid and 0.4 mg of vitamin B12; 40 mg of vitamin B6; or placebo. The primary end point during a median follow-up of 40 months was a composite of recurrent myocardial infarction, stroke, and sudden death attributed to coronary artery disease.

CONCLUSIONS: Treatment with B vitamins did not lower the risk of recurrent cardiovascular disease after acute myocardial infarction.

In pazienti reduci da infarto del miocardio il trattamento con vitamine del gruppo B ed acido folico non riduce il rischio di recidiva di patologie cardiovascolari nonostante una riduzione media dei livelli di omocisteina del 27%

N Engl J Med. 2006 Apr 13;354(15):1567-77. Epub 2006 Mar 12.

Homocysteine lowering with folic acid and B vitamins in vascular disease.

Lonn E, Yusuf S, Arnold MJ, Sheridan P, Pogue J, Micks M, McQueen MJ, Probstfield J, Fodor G, Held C, Genest J Jr; Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators.

Population Health Research Institute, Hamilton General Hospital, McMaster University, and the Department of Medicine, Division of Cardiology, Hamilton Health Sciences, Hamilton, Ont. lonnem@mcmaster.ca

METHODS: We randomly assigned 5522 patients 55 years of age or older who had vascular disease or diabetes to daily treatment either with the combination of 2.5 mg of folic acid, 50 mg of vitamin B6, and 1 mg of vitamin B12 or with placebo for an average of five years. The primary outcome was a composite of death from cardiovascular causes, myocardial infarction, and stroke.

CONCLUSIONS: Supplements combining folic acid and vitamins B6 and B12 did not reduce the risk of major cardiovascular events in patients with vascular disease. (ClinicalTrials.gov number, NCT00106886; Current Controlled Trials number, ISRCTN14017017.).

La supplementazione di vitamine del gruppo B ed acido folico non riduce il rischio di recidiva di patologie cardiovascolari in pazienti con malattie cardiovascolari

American Heart Association.
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Homocysteine, Folic Acid and Cardiovascular Disease

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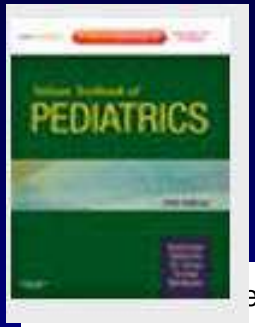
AHA Recommendation

The American Heart Association has not yet called hyperhomocysteinemia (high homocysteine level in the blood) a major risk factor for cardiovascular disease. We don't recommend widespread use of folic acid and B vitamin supplements to reduce the risk of heart disease and stroke. We advise a healthy, balanced diet that's rich in fruits and vegetables, whole grains, and fat-free or low-fat dairy products. For folic acid, the recommended daily value is 400 micrograms (mcg). Citrus fruits, tomatoes, vegetables and grain products are good sources. Since January 1998, wheat flour has been fortified with folic acid to add an estimated 100 micrograms per day to the average diet. Supplements should only be used when the diet doesn't provide enough.



Chapter 472 – Hereditary Predisposition to Thrombosis

Leslie J. Raffini,
J. Paul Scott

e frequently asked to evaluate children for inherited risk factors for thrombosis with symptomatic thrombosis or asymptomatic children who have relatives affected with either thrombosis or thrombophilia. **The clinical utility of thrombophilia testing is debated, both in adults and children**.

Thrombophilia testing rarely influences the acute management of a child with a thrombotic event. The association between inherited thrombophilia and pediatric thrombosis varies based on the clinical scenario: children with unprovoked thrombotic events have a high prevalence of inherited defects, while the role of thrombophilic defects in children with catheter-related thrombotic events is questionable. **Although some thrombophilic defects are associated with a higher risk of recurrent venous thromboembolism in children, how to use these results to guide the duration of therapy has not been determined. Prospective longitudinal analyses of such patients to determine outcome and response to treatment as well as the impact of known thrombophilic states on these outcomes are clearly needed**.

The decision to perform thrombophilia testing in an otherwise healthy child with a family history of thrombosis or thrombophilia should be carefully considered, weighing the potential advantages and limitations of such an approach. Given that the absolute risk of thrombosis in children is extremely low (0.07/100,000), it is unlikely that an inherited thrombophilia will have any impact on clinical decision-making for a young child. **The risk of thrombosis increases with age, so that identification of a thrombophilic defect in an adolescent may guide thromboprophylaxis in high-risk situations (lower extremity casting or prolonged immobility), inform the discussion about estrogen-based contraceptives, and may promote lifestyle modification to avoid behavioral prothrombotic risk factors (sedentary lifestyle, dehydration, obesity, and smoking). Limitations of such testing include the cost as well as the potential for causing unnecessary anxiety or false reassurance.**

CONCLUSIONI

Ma come agire nei pazienti con più o meno importanti rischi “ aggiuntivi” (ipercolesterolemia, fumo, anticoncezionali, diabete , etc.) ?