Recurrent thrombosis, not anti-phospholipid syndrome…….

G M Connolly[1], K E Ryan[1], C M Loughrey[1]

[1]Department of Clinical Biochemistry, Royal Victoria Hospital, Belfast

Case History

We present the case of a 32-year-old woman who presented with a post-partum left parietal lobe infarct. Her past medical history included two miscarriages, a post-partum DVT and a stillbirth at 5 months due to placental clots. She had normal intellectual development and normal habitus. She had been diagnosed in another centre with antiphospholipid syndrome.

Investigation

In our centre, young patients presenting with a stroke have a panel of tests requested to investigate for potential cause. This includes a request for total homocysteine.

In this case, the patient's total homocysteine was grossly elevated at 411 µmol/l (<12). Further assessment revealed normal vitamin B12, folic acid and urine organic acids (methylmalonic acid). Plasma amino acids demonstrated a high plasma methionine 327 µmol/l (22-32) suggesting a diagnosis of classical homocystinuria due to cystathionine beta-synthase (CBS) deficiency.

Homocysteine metabolism

Homocysteine, a sulfhydryl-containing amino acid, is synthesized as an intermediate metabolite from **methionine** metabolism. It is converted to cysteine via the transsulfuration pathway or re-synthesized back to methionine via the re-methylation pathway (Figure1).

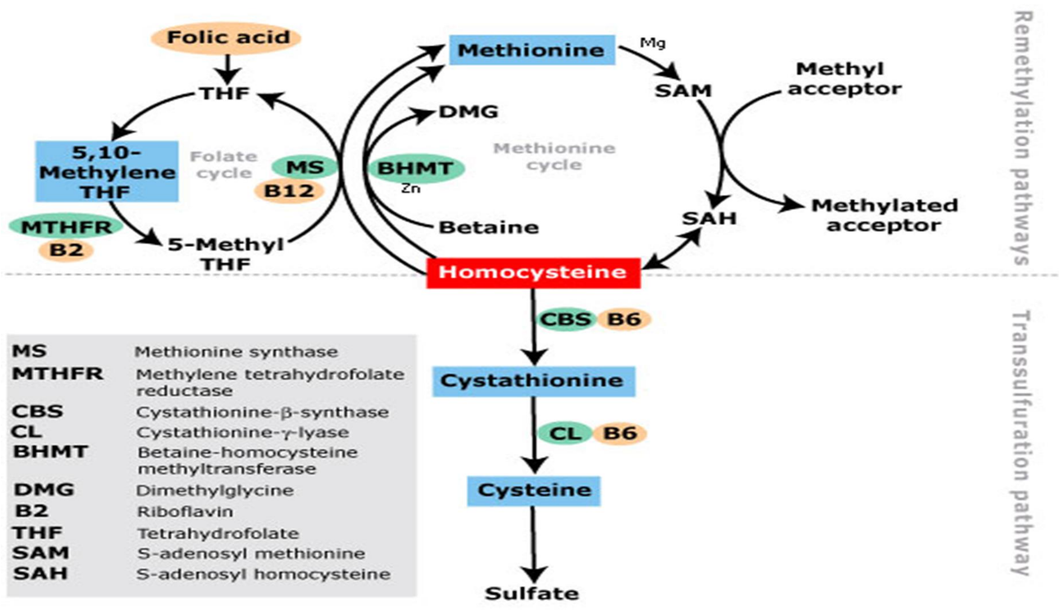

Figure 1 Homocysteine metabolism pathways

Homocysteine can be increased through defective metabolism of methionine, due to genetic defects of enzymes responsible for homocysteine metabolism or deficiencies of cofactors involved in these pathways (vitamins B6 (pyridoxine), B12 and folate) (Figure 1).

Severe hyperhomocysteinaemia with high methionine is seen in CBS deficiency.

Homocystinuria

CBS deficiency (or classical homocystinuria) is a rare autosomal recessively inherited disorder, first described in Belfast in 1962 (Carson and Neill). It is caused by mutations in a gene that regulates the production of the CBS enzyme (Figure 1).

Patients with CBS deficiency show a wide spectrum of severity and age at presentation; some have a severe childhood-onset multisystem disease, whilst others are asymptomatic into adulthood. The main clinical features are a predisposition to thromboembolism, lens dislocation, osteoporosis, a 'marfanoid' habitus and learning difficulties.

The CBS enzyme requires vitamin B6 (pyridoxine) as a cofactor. Some patients with CBS deficiency are extremely sensitive to pyridoxine, achieving dramatic reductions in homocysteine with pyridoxine. Pyridoxine-responsive patients generally have a milder phenotype and a later onset than individuals with pyridoxine-unresponsive homocystinuria.

Case Update

The patient was given a trial of pyridoxine and her homocysteine fell dramatically to 40 µmol/l (<12) on pyridoxine 500mg daily. This supported a diagnosis of pyridoxine responsive homocystinuria.

Genetic testing has confirmed a mutation in the CBS gene. A second mutation has not yet been identified.

The patient's homocysteine remains well controlled on pyridoxine, she has had no further thrombotic events and has had a further pregnancy and delivery without complication.

Discussion

Homocystinuria is a rare inherited disorder causing gross elevation in blood homocysteine. Untreated it is a cause of recurrent, potentially life threatening, thrombotic events. However, as this case demonstrates, pyridoxine treatment in individuals with pyridoxine-responsive homocystinuria is straightforward and effective, significantly reducing homocysteine and associated complications.

Conclusion

This case demonstrates the importance of measuring blood homocysteine concentrations in anyone presenting with recurrent or unexplained thrombosis to ensure correct diagnosis and enable institution of effective treatment.