Premature vascular disease and thrombosis are recognized complications in homocystinuria. Vascular disease in patients with homocystinuria affects both arterial and venous systems, with venous thrombosis as the major cause of death (Mudd et al 1985). Histologically, the arterial disease is characterized by intimal and medial smooth-muscle hyperplasia, with fibrosis and thickening of the elastic lamina, but lipid deposition is usually not observed (Gibson et al 1964). This contrasts with the classical appearance of atheromatous vascular disease in the general population. Relatively little is known about possible disturbances to lipid metabolism in patients with homocystinuria. We report observations on lipids and lipoproteins in a group of patients being treated and monitored for homocystinuria.

METHODS

Fasting blood samples were collected from 10 patients with homocystinuria (6 male and 4 female) with a mean age of 26 years, range 6–66 years. Nine of these patients had cystathionine β-synthase deficiency (McKusick 236200), 5 of whom were pyridoxine responsive. The remaining patient had a functional methionine synthase defect. A total of 41 fasting blood samples were collected from the 10 patients over a period of 6 months as part of their routine monitoring. Samples were frozen at −70°C until required for analysis.

Plasma total homocysteine (tHcy) was measured by HPLC with fluorescence detection (Spaapen et al 1992). Plasma total cholesterol and triglycerides were determined by enzymatic methods using a Vitros 250 Dry Chemistry Analyser (Ortho Clinical Diagnostics). Apo A1, Apo B and Lp(a) were measured by rate nephelometry using a Beckman Array 360 Instrument (Beckman Instruments).
Regression analysis was performed to explore associations between lipid variables and tHcy. Statistical significance was accepted at the 95% confidence interval ($p < 0.05$).

RESULTS

There was a significant negative association between plasma total cholesterol and tHcy, and also between plasma triglycerides and tHcy (Figure 1A and B). Furthermore, serial samples ($n = 16$) taken from a single patient with pyridoxine-responsive homocystinuria from a period of non-compliance to a period of control showed an even stronger association between plasma total cholesterol and triglycerides and tHcy ($r = -0.82$, $p < 0.001$, $r = -0.71$, $P < 0.001$), respectively.

There was an inverse association between Apo A1 and tHcy ($r = -0.46$, $p < 0.005$) and between Apo B and tHcy ($r = -0.31$, $p < 0.025$). This association was also evident between Apo A1 and Apo B and tHcy in the single patient (Figure 1C and D). No association was observed between Lp(a) and plasma tHcy.

Lipids in homocystinuria

DISCUSSION

In these patients, who were receiving treatment for homocystinuria, there was a strong inverse relationship between circulating lipids (cholesterol or triglycerides) and plasma tHcy. This observation applied between individuals and also for an individual from whom samples were taken on different occasions. Plasma Apo A1 is the main protein of high-density lipoprotein (HDL) and Apo B is the main protein of low-density lipoprotein (LDL) and they may be used as surrogate markers of these lipoproteins, which were not measured directly in this study. The inverse association between Apo A1 and Apo B and tHcy indicates that high tHcy was characterized by both low HDL and low LDL concentrations in plasma. Cholesterol is transported in both HDL and LDL and thus the reduced cholesterol concentrations can be accounted for by a reduction in both lipoprotein fractions. The association between low triglycerides and low Apo A1 is more unusual. In most pathophysiological settings HDL (and hence Apo A1) varies inversely with triglyceride concentrations. This is generally considered to be due to the effect of cholesterol ester transfer protein, which has enhanced activity in the presence of hypertriglyceridaemia, leading to transfer of triglyceride into HDL and subsequently faster clearance of HDL/Apo A1 (Rader and Ikewalei 1996). The link between low Apo A1 and low triglycerides found here indicates that an alternative mechanism may be operating in homocystinuria.

Lp(a) is an LDL-like lipoprotein with additional protein component (Apo(a)) attached by a disulphide bond. The possibility of an interaction with homocysteine is of interest particularly in view of the suggestion from in vitro data that homocysteine may enhance fibrin binding of Lp(a), thereby enhancing thrombus formation (Harpel et al 1992). However, in this study no association between Lp(a) and tHcy was found.

The explanation for the results observed is unclear. It is not possible to determine whether the relationship between tHcy and lipoproteins is one of cause and effect. Indeed, the few experimental studies to examine this aspect have found that the administration of homocysteine-thiolactone to animals elevated plasma triglycerides, cholesterol and LDL but did not elicit changes in HDL (Gaggi and Gianni 1973; McCully et al 1990). Irrespective of the mechanism, it is tempting to speculate that reduced plasma lipoproteins may contribute to the lack of arterial lipid deposition in patients with homocystinuria. These findings may help to explain the surprisingly low incidence of vascular events reported in deficient patients with homocystinuria who are receiving treatment (Wilcken and Wilcken, 1997).

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