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HYPERLIPIDAEMIAS

Not so long ago the hyperlipidaemias could be simply thought of in 2 groups: hypercholesterolaemia, which may be primary or secondary, and lipaemia, in which the plasma is milky. The chief significance of hypercholesterolaemia is that it is one factor predisposing to atherosclerosis in the coronary and other arteries.[1] It is also a useful biochemical sign of hypothyroidism, nephrosis and obstructive jaundice. Lipaemia results from greatly increased concentration of triglycerides in plasma. The mechanisms producing lipaemia have not been well understood and the relationship of this hypertriglyceridaemia to coronary disease is still debatable.[2] It was known that plasma cholesterol and triglycerides can sometimes be increased together, which constituted a third group, mixed hyperlipidaemia.

From the clinician's viewpoint, the hyperlipidaemias are analagous to other metabolic disorders like diabetes mellitus and hyperuricaemia. Severe lipaemias may cause acute symptoms of abdominal pain and eruptive xanthomas for which immediate treatment is clearly needed as it is for diabetic ketosis and gout. More often, however, the problem is the possibility of insidious development of long-term complications. Atherosclerotic disease in hyperlipidaemias corresponds to the many late complications of diabetes and to the nephropathy of hyperuricaemia. The patient with hyperlipidaemia usually feels well, though xanthomas are sometimes detectable on examination. Because no doctor wants to prescribe a treatment that is worse than the disease, it is not surprising that management of hyperlipidaemias varies greatly between individual doctors. An estimate of the patient's chances of developing atherosclerosis and also how he responds to treatment must play a large part in determining whether prophylactic treatment is continued indefinitely or abandoned after a short trial.

It is now known that there are more than two different types of hyperlipidaemia, and they are caused by different mechanisms. They respond differently to the several available treatments and may carry different atherogenetic tendencies. For this reason it is important that practitioners should be aware of the more complicated classification of hyperlipidaemias which has been developed in recent years, particularly by Fredrickson and his associates at the National Heart Institute, Bethesda, USA.

Fredrickson divides the hyperlipidaemias into 5 types. His classification was originally worked out for the primary or genetic hyperlipidaemias.[3] The secondary hyperlipidaemias can be roughly fitted into the same 5 types.[4]

Type I hyperlipidaemia is dietary fat-induced lipaemia. There is a pure hypertriglyceridaemia. The increased triglyceride is carried on chylomicrons which are present in fasting plasma. It is a rare disease, which usually presents in childhood with abdominal pain, hepatosplenomegaly, or pancreatitis. Small transient skin xanthomas may appear (eruptive xanthomas). Treatment is a very low fat (high carbohydrate) diet, which could be supplemented with medium-chain triglycerides. It does not seem to predispose to coronary disease.

Type II hyperlipidaemia is pure hypercholesterolaemia. The increased cholesterol is carried on low-density lipoprotein, the ordinary β-lipoprotein. Depending on the degree of increased cholesterol and its duration there may be xanthomas. The most important place to examine is the Achilles tendons. Detection of early thickening requires experience. These tendons should be palpated as part of every full medical examination. Primary hypercholesterolaemia is a fairly common genetic disease, inherited as a dominant. Hypercholesterolaemia can be found in early childhood in affected members of a family. The disease predisposes to atherosclerosis but not in every family. The best treatment is the polyunsaturated fat, low cholesterol diet. It is as effective as any other and without known side-effects. Type II hyperlipidaemia tends to be rather resistant to any type of treatment, especially when tendon xanthomas have already developed.[5] Diet may need to be supplemented with clofibrate (Atromid) or D-thyroxine (4 - 8 mg./day, if the patient does not have angina) or cholestyramine resin (Cuemid). Each of these treatments acts in different ways, so they can be used in any combination with the hope of synergistic effect.

Secondary type II hyperlipidaemia is found in hypothyroidism, obstructive jaundice and the nephrotic syndrome. Treatment is largely that of the underlying disease.

Type III hyperlipidaemia is less common. The picture is similar to that of type II, except that xanthomas may be seen as creamy streaks in the palmar digital creases. Triglycerides are increased in the plasma to about the same concentration as cholesterol. On paper electrophoresis there is a characteristically broad β-lipoprotein band, the increased low-density lipoprotein merging with increased very low density lipoprotein, which runs in the pre-β position. The disorder seems to predispose to atherosclerosis in the same way as type II. Unlike type II, treatment is much easier. Response can be dramatic to diet or clofibrate.[6] The principle of diet therapy for this type is reduction of body-weight to normal, where necessary, followed by the polyunsaturated fat, low cholesterol diet.

Type IV hyperlipidaemia is endogenous lipaemia. This and type II are the two commonest hyperlipidaemias. Plasma triglycerides are increased more than cholesterol in type IV. The increased lipid is carried on very low density

lipoprotein. On paper electrophoresis there is therefore a pre-β lipoprotein band in addition to and separate from a normal β-lipoprotein band. In severe cases the plasma is lipaemic, with moderate hypercholesterolaemia. In milder forms the plasma is only faintly turbid and cholesterol may be within normal limits. Such a condition will therefore be missed unless plasma triglycerides are determined chemically.

Type IV hyperlipidaemia is caused by increased hepatic synthesis of triglycerides, which are secreted into plasma on very low density lipoproteins. This occurs when mobilization of free fatty acids from adipose tissue is increased. Secondary type IV hyperlipidaemia is to be expected in uncontrolled insulin-requiring diabetics with ketosis. It can also occur in obese, middle-aged diabetics. A number of other conditions can be associated with this type of hyperlipidaemia. There may be gross lipaemia with pancreatitis and sometimes alcoholism. Patients with nephrotic syndrome and hypothyroidism sometimes have this type of lipid abnormality rather than type II. Mild degrees of the same changes are seen in pregnancy and in some women taking oral contraceptives.

Primary type IV hyperlipidaemia is quite common in middle-aged men. Affected individuals tend to be obese and to have abnormal glucose tolerance. The disorder is often familial, but it is not clear at present whether this has a genetic or an environmental explanation.

As with type I, patients with gross lipaemia may present with eruptive xanthomas. These resolve rapidly when the hypertriglyceridaemia is reduced. Type IV patients often have associated evidence of atherosclerosis. But unlike hypercholesterolaemia, no prospective trial has yet been done to see if people with pure hypertriglyceridaemia are more likely to develop coronary disease. Such a trial has been started in Stockholm and the results will be awaited with interest.

The best treatment of type IV is a weight-reducing, low-carbohydrate diet. When body-weight is normal, the reduced dietary carbohydrate may be replaced by polyunsaturated fats. If reduction of dietary sucrose has any role to play in prevention of atherosclerosis, it is in this type of hyperlipidaemia. The lipid-lowering drugs of most value in type IV are those which have more effect on endogenous plasma triglycerides than on plasma cholesterol, namely clofibrate and nicotinic acid.

Type V hyperlipidaemia is characterized by increase of chylomicrons together with very low density (pre-β) lipoproteins. It thus appears to be a biochemical combination of type IV and type I. It is less common than type IV, commoner than type I. It may represent a more severe form of type IV hyperlipidaemia, in which delayed clearing of chylomicrons after eating fat is superimposed on endogenous lipaemia. It occurs in the same diseases as type IV hyperlipidaemia—diabetic ketosis, nephrosis, pancreatitis, alcoholism, etc. There may be attacks of abdominal pain and hepatosplenomegaly in addition to the clinical features of type IV. When the disorder is primary, low-calorie diets are usually effective. Dietary fat may have to be low to start with, to prevent attacks of abdominal pain. Clofibrate may be useful.

Although Fredrickson's classification is very valuable in understanding and management of hyperlipidaemias, some cases cannot be easily fitted into any of the five types.[5,7] Furthermore a new, rare type of hyperlipidaemia has just been described from Scandinavia.[8] In this disorder, familial plasma lecithin: cholesterol acyltransferase deficiency, there is moderate lipaemia with clinical features including corneal opacity and proteinuria. Though the total plasma cholesterol is somewhat increased, it is abnormal in that most of it is not esterified. Here we already have a sixth type of hyperlipidaemia, and further types may yet be characterized as understanding of biochemistry enlarges.

From the practical point of view there are some details of technique which deserve attention before hyperlipidaemia can be diagnosed. Plasma cholesterol is fairly stable and most biochemical pathology laboratories can measure it. The level is not affected by meals or by ordinary daily activities. However, plasma cholesterol falls considerably for 2 or 3 weeks after a myocardial infarction.[9] To decide if such a patient has underlying hypercholesterolaemia, one should either use blood taken within hours of the infarct or else wait until about a month after and take the blood when the patient is on an ordinary diet. Plasma cholesterol varies with the seasons, at least in the northern hemisphere, being lowest in the summer. This phenomenon can lead to confusion if the effect of a particular treatment is being followed.

There are two practical difficulties with measuring plasma triglycerides. Blood must be taken after a 12-hour fast, because levels increase after a meal containing even small amounts of fat. This means that if triglycerides are to be measured in outpatients they should miss breakfast before they come to see the doctor, like diabetics. Secondly, the chemical methods for plasma triglycerides are rather more time-consuming than cholesterol methods and many pathology laboratories do not yet offer this service. Gross hypertriglyceridaemia can be recognized merely by looking at a plasma or serum sample, but for lesser grades and for following treatment a chemical determination is necessary. It is likely that more laboratories will set up the method as interest grows in this important group of metabolic disorders.

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