Clinical Reports

Retinal pigment epithelial change and partial lipodystrophy

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Summary: Cuticular drusen and retinal pigment epithelial changes were found incidentally in a 27 year old Lebanese woman during assessment of partial lipodystrophy. Her vision was normal despite involvement of both maculae. The patient had hypocomplementaemia, but serum C3 nephritic factor was absent and renal function was normal. She had impaired glucose tolerance and a continuous infusion of glucose with model assessment (CIGMA) test revealed low normal tissue insulin sensitivity and high normal pancreatic beta cell function. Mild fasting hypertriglyceridaemia (2.0 mmol/l) may have been secondary to impaired insulin sensitivity. Endocrine function was otherwise normal apart from a completely absent growth hormone response to adequate hypoglycaemia. The simultaneous occurrence of partial lipodystrophy and retinal pigmentary epithelial and basement membrane changes appears to be a newly recognized syndrome.

Introduction

Partial lipodystrophy, first described over 100 years ago1 is one of several poorly-understood disorders characterized by loss of subcutaneous fat.2-3 In its most common form, partial lipodystrophy affects the face, trunk and upper limbs in a 'cephalothoracic' distribution. There may, however, be excessive fat deposition in the lower half of the body.2 The patients are usually young females with no family history of abnormal fat loss.

Partial lipodystrophy is frequently associated with hypocomplementaemia, hyperlipidaemia and abnormal glucose tolerance.2,4-12 A variety of other renal, endocrinological, neurological and immunological diseases have also been reported in patients with this and other lipoatrophic conditions.

We report the case of a female patient with cephalothoracic partial lipodystrophy and retinal pigment epithelial change. In addition to hypocomplementaemia and hypertriglyceridaemia, our patient also had impaired glucose tolerance, and this was investigated using the newly-developed CIGMA (continuous infusion of glucose with model assessment) technique.13

Case report

A 27 year old single Lebanese woman was referred for assessment of partial lipodystrophy. After a 3 year period of unexplained, progressive and generalized weight loss from the age of 7 years, she began to notice that subsequent weight gain was accompanied by an increase in subcutaneous fat only below waist-level. At the age of 16 years, she attained her maximum body weight and height of 62 kg and 1.52 m respectively. Her weight then fell to 45 kg during her early twenties before stabilizing close to that at the time of referral (57 kg). The abnormal distribution of fat remained during this time.

She was otherwise symptom free. She was unaware of any family member ever having suffered from lipodystrophy, diabetes mellitus or renal disease.

On examination, she had marked lipoatrophy involving the face, arms and trunk down to the level of the iliac crests. There was excessive subcutaneous fat deposition over both legs. There were no stigmata of diabetes, and acanthosis nigricans was not present. Her visual acuity and peripheral visual fields were normal.

Ophthalmoscopy revealed normal optic discs. However, bilateral diffuse granular pigmentation was seen and both maculae were involved. Retinal blood vessels were attenuated and pigment sheathing of the vessels was present in the far
resting electrocardiogram, and ward urinalysis (Multistix) and urine microscopy, were all normal. Creatinine clearance was 140 ml/min and there was no detectable protein in a 24 hour urinary collection. Her fasting serum cholesterol concentration was normal (4.2 mmol/l) but her fasting triglyceride concentration was raised (2.0 mmol/l; reference range for females <1.5 mmol/l).

Symptomatic insulin-induced hypoglycaemia (0.3 U/kg body weight i.v.: trough plasma glucose <1.0 mmol/l) provoked a normal rise in plasma cortisol (to 834 nmol/l) but a growth hormone (GH) response to this stimulus was absent (maximum serum growth hormone concentration 2.4 mU/l). A previous attempt to induce symptomatic hypoglycaemia using 0.15 U insulin/kg was unsuccessful (plasma glucose concentration >2.0 mmol/l throughout). A total serum thyroxine concentration was normal, and sex steroid concentrations were commensurate with age and stage of menstrual cycle.

No organ-specific autoantibodies were detected and C3 nephritic factor was absent. Serum immunoglobulin concentrations were normal but complement activities were low (C4 86%, C3 33%, and CH50 24% of pooled normal human serum).

The fasting plasma glucose concentration was normal (mean ± s.d., 5.4 ± 0.3 mmol/l, n = 5) but a 75g oral glucose tolerance test (OGTT) showed impaired glucose tolerance (60- and 120-minute plasma glucose concentrations 13.3 and 9.4 mmol/l respectively). A serum fructosamine level was normal (2.3 mmol/l; reference range <2.8 mmol/l).

The patient also had a CIGMA test in which a constant infusion of 5 mg glucose/kg ideal body weight/minute over an hour achieves physiological plasma glucose concentrations and allows quantitation of pancreatic beta cell function and tissue insulin sensitivity relative to those in normal control subjects. The plasma glucose concentration rose from 5.3 mmol/l to 9.1 mmol/l (normal end-infusion range 6.1–9.3), and the mean plasma insulin concentration from 12.9 mU/l to 43.6 mU/l (normal end-infusion range 8.5–44.6), and the mean plasma C-peptide concentration from 0.77 nmol/l to 1.34 nmol/l (normal end-infusion range 0.59–2.14). The CIGMA-derived insulin sensitivity was low normal (56% reference range for young adults 41–214) and pancreatic beta cell function was high normal (135%; reference range 27–224).

Discussion

Partial lipodystrophy is a rare condition, and its manifestations can extend beyond the distressing cosmetic effects with which most patients present.
Consequently, patients with this and other forms of lipoatrophy warrant full initial assessment and careful follow-up, even if they are asymptomatic when first seen.

Carbohydrate intolerance in association with partial lipodystrophy has been reported by many authors. Although a proportion of these cases have had an unusual, non-cephalothoracic distribution of partial subcutaneous fat loss together with a definite inheritance pattern, a common finding is of increased fasting and stimulated serum insulin concentrations. This suggests insulin resistance and, when frank diabetes develops, large doses of insulin are required.

Our patient had high normal fasting and stimulated plasma insulin concentrations, low normal insulin sensitivity assessed by CIGMA, and required a large intravenous insulin dose to achieve adequate hypoglycaemia during pituitary stimulation testing. Together with glucose intolerance during OGTT, these results indicate that she has tissue insensitivity to insulin. Although there is evidence against an intrinsic abnormality of fat cells from lipodystrophic patients, her body mass index has increased from 19.5 to 24.7 kg/m² in a matter of years and further weight gain could result in worsening of glucose intolerance.

Our patient's pancreatic beta cell function was greater than the mean value for healthy young adults. The sensitivity of the CIGMA test in detecting even mildly impaired beta cell function appears good but in our patient it was normal.

Mild fasting hypertriglyceridaemia in our patient was more than could be expected for her degree of glucose intolerance. Hypertriglyceridaemia has been consistently found in association with partial lipodystrophy, even in patients with normal oral glucose tolerance. Since insulin reduces hepatic triglyceride release, hypertriglyceridaemia is probably a further manifestation of insulin resistance.

Other tests of endocrine function were normal, apart from her completely absent GH response to symptomatic hypoglycaemia. Impaired GH responses have been found in obese and diabetic subjects, but our patient would not fall into either group. Furthermore, GH responses in 'typical' cases of partial lipodystrophy have previously been found to be normal or exaggerated, the latter finding having been suggested as a possible cause for some of the manifestations of the disorder. The mechanism for our patient's absent GH response remains unclear.

Patients with partial lipodystrophy are prone to develop mesangiocapillary glomerulonephritis, with low serum complement activity and detectable levels of serum C3 nephritic factor. However, there is evidence that hypocomplementaemia can sometimes precede overt nephritis by many years. Furthermore, the development of renal impairment in those who become C3 nephritic factor positive may initially be clinically inapparent. This means that patients such as ours should be assessed regularly from a renal point of view.

The patient described in this report illustrates a further association which should be considered in the management of such patients. The extensive deposition of material in the basement membrane of the retina is probably not coincidental and might be analogous to glomerular basement membrane changes seen in the mesangiocapillary glomerulonephritis which can be associated with partial lipodystrophy. Alternatively, the combination of retinal abnormalities, partial lipodystrophy with impaired insulin sensitivity, and hypocomplementaemia might be due to deletion of a short segment of chromosome.

Retinal pigmentary epithelial change was seen to involve both maculae in our patient. However, the fovea was unaffected, her central vision was normal, and no peripheral field defect was detected. The normality of her visual function suggests that her visual prognosis is good.

The young woman described in this report illustrates many of the features of a 'typical' patient with progressive partial lipodystrophy. In addition, she has evidence of retinal pigment epithelial and basement membrane changes, a hitherto unpublished association. Although little is known of the aetiology and pathogenesis of the lipoatrophic disorders, a careful characterization of their clinical, biochemical and metabolic manifestations may provide valuable clues for future study.

Acknowledgements

We are grateful to Professor I.S. Salti of the American University, Beirut, for referring this patient.

*During the preparation of this manuscript we became aware of similar cases (case presentation at Section of Ophthalmology, Royal Society of Medicine. Duval et al. Br J Ophthalmology, in press).

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Postgrad Med J 1988 64: 871-874
doi: 10.1136/pgmj.64.757.871

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