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Dunnigan-Kobberling syndrome: an autosomal dominant form of partial lipodystrophy

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Summary

Dunnigan-Kobberling syndrome is a form of partial lipodystrophy characterized by sparing of the face.[1] Despite descriptions of six families since 1974, details of total body adipose tissue distribution and studies of carbohydrate and fat metabolism are lacking. The mode of inheritance also remains unclear, with most authors favouring an X-linked dominant transmission lethal in the hemizygous male.[2,3] We examined 23 members of a family, of whom at least eight had partial lipodystrophy. Auxological evaluation and cross-sectional imaging showed absence of subcutaneous fat, presence of adipose tissue inside the body cavities, and skeletal muscle hypertrophy. Biochemical evaluation identified insulin resistance but revealed inadequate suppression of non-esterified fatty acids. In this family, male-to-male transmission supports an autosomal dominant mode of inheritance for Dunnigan-Kobberling syndrome.

Introduction

Fat is found predominantly in the adipose tissue and liver. In the form of triglycerides, it is the major store of energy in the body. It also acts as insulation from the cold and, in the case of brown fat, can be used to generate heat by the uncoupling of oxidative phosphorylation. The pattern of distribution and total amount of adipose tissue is dependent on genetic, hormonal and environmental factors.[4,5,6] Obesity (excess body fat), can be defined as body mass index over 30 kg/m^2, triceps plus subscapular skinfold above 45 mm in males and 69 mm in females, or body fat more than 25% of total body weight in males or 35% in females. In contrast, when there is a regional or global absence of adipose tissue, the individual is said to be lipodystrophic.

At least four inherited or sporadic clinical syndromes of lipodystrophy have been described. All are rare. Seip-Berardinelli syndrome, initially reported in 1954[7] is characterized by generalized lipodystrophy, hyperlipidaemia, hepatomegaly and insulin-resistant, non-ketotic diabetes mellitus. Males and females are equally affected by this autosomal recessive condition, which manifests before the age of two years.

Cephalothoracic lipodystrophy involves lipodystrophy of the face arms and upper torso and is associated in some with mesangiocapillary glomerulonephritis and the presence of C3 nephritic factor or homozygous C3 deficiency.[8,9] Predominance of females is recognized and, again, there is an association with non-ketotic diabetes mellitus and hyperlipidaemia. A proportion of these cases are autosomal recessive while the rest are likely to be sporadic, some occurring after an infective episode.

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Lawrence syndrome, first described in 1946,[10] is a sporadic form of generalized lipodystrophy with hepato(spleno)megaly and insulin-resistant diabetes mellitus. It is more common in females and its onset is at adolescence.

Dunnigan[1] and Kobberling[11] described a face-sparing lipodystrophy with involvement of the limbs and variable involvement of the trunk but with normal or excessive fat on the face and neck. Acanthosis nigricans was a universal finding and the presence of xanthomata was common. Metabolic abnormalities in the four published families ranged from mild hyperlipidaemia and asymptomatic impaired glucose tolerance to insulin-treated non-ketotic diabetes mellitus and severe hyperlipidaemia leading, in one case, to acute pancreatitis and in some other cases to early deaths secondary to complications of diabetes. There was no organomegaly in any of these individuals. No males with Dunnigan-Kobberling syndrome have been described in detail. Reardon *et al.*[12] identified a male infant with lipodystrophy of the limbs and trunk born to normal parents and with a normal male sibling. This child showed no biochemical evidence of insulin resistance. In addition, his liver and spleen were enlarged. The sporadic nature, early onset and organomegaly in this child make the diagnosis of Dunnigan-Kobberling syndrome unlikely. Reference was made to an affected male, the father of a female proband with classical features of Dunnigan-Kobberling syndrome.[13] This individual was described to be of athletic build with an elevated fasting triglyceride of 6.7 mmol/l, normal fasting blood glucose and elevated fasting insulin level. No other affected male was identified in this kindred. The paucity of affected males led Dunnigan and Kobberling to conclude that the inheritance of this form of partial lipodystrophy to be X-linked dominant with lethality in the hemizygous state.[2]

We describe a single extended family with the Dunnigan-Kobberling phenotype segregating as an autosomal dominant trait as evidenced by male-to-male transmission. There were at least eight lipodystrophic individuals including three males with the classical features of Dunnigan-Kobberling syndrome. The phenotype is described by auxology and whole-body magnetic resonance imaging. Data from oral glucose tolerance testing are presented, confirming the presence of insulin resistance and incomplete suppression of serum non-esterified fatty acids.

Methods

The propositus presented in 1993 at the age of 24, complaining of dark, thickened skin in the axillae and groins consistent with the clinical diagnosis of acanthosis nigricans. She had been noted to have impaired glucose tolerance during a previous pregnancy in 1988, but had not required insulin therapy. During her second pregnancy in 1995, she developed gestational diabetes and required insulin therapy, her glucose tolerance returning to normal in the puerperium. Physical examination revealed lipodystrophy over the trunk and limbs with sparing of the face, neck and hands, with visible subcutaneous veins on the arms and legs. The muscles of the shoulder and hip girdles appeared to be hypertrophied. Acanthosis nigricans was present in mild degree in the axillae and inguinal regions. Her blood pressure was 120/80, there was no palpable organomegaly, no hirsutism and urinalysis was unremarkable. She described several female family members with a similar body habitus to her own and stated that her brother had a very athletic build despite performing little exercise and that two of her paternal aunts suffered from diabetes mellitus.

Twenty-three members of this pedigree have since been examined by one of the authors (SJ) in order to assign affected status. Individuals were considered lipodystrophic if there was clinical absence of subcutaneous fat on the limbs and unaffected if there was obvious visible and palpable subcutaneous fat on the limbs. All individuals considered affected or with an indeterminate phenotype attended hospital for detailed clinical examination as well as auxological evaluation including weight, height, waist and hip measurements and mid arm muscle circumference. Skinfold thickness was estimated with a Harpendon caliper in the scapular, umbilical and supra-iliac regions as well as over the triceps and biceps muscles of the non-dominant arm. All subjects were asked to fast from 8pm on the day prior to attending hospital and asked to refrain from smoking. Any insulin therapy or oral hypoglycaemic agents were omitted on the morning of the test.

A forearm vein was cannulated half an hour before the glucose tolerance test was begun. WHO criteria[14] were used to define diabetes, impaired glucose tolerance and normal glucose tolerance. A 75 g oral glucose tolerance test was performed with estimations of plasma glucose, insulin, intact proinsulin and 32/33 split proinsulin, and serum non-esterified fatty acids at times 0, 60 and 120 min. Samples of sera and plasma were immediately separated and stored at −70°C. Plasma glucose was measured by a hexokinase method. Plasma insulin level was determined by two-site immunometric assays with either ^{125}I or alkaline phosphatase labels. Plasma intact and split proinsulin is estimated by a time-resolved fluorescence immunometric method (Taylor K. *et al.*, in preparation). Plasma NEFA measurements were determined enzymically, based on the activity of acyl-CoA synthetase (Boehringer

Mannheim). The assay has a between-assay coefficient of variation of 10% at 0.4 mmol/l and 6% between 1.2 and 2.3 mmol/l.

Cross-sectional imaging

Two lipodystrophic subjects, III:9 and III:10, underwent whole-body magnetic resonance imaging. Axial T1-weighted images were obtained with the subject lying supine in a 1.0 tesla Siemens Magnetom imaging device. T1-weighting was chosen as adipose tissue and other structures containing fat give a high signal intensity.

All parts of this study received approval from the Leicestershire Ethics Committee.

Results

Twenty-four family members (9 male) were contacted, of whom twenty-three (8 male) gave consent to be seen (Figure 1). In addition, historical records of individual I:2 were reviewed, including family photographs. Nine of the individuals examined (3 male) satisfied the above criteria for the Dunnigan-Kobberling phenotype (Figure 2). In addition, one 8-year-old male, IV:5, with a lipodystrophic mother had symmetrical lipodystrophy confined to the legs. One twenty-year old male, III:3, had an indeterminate phenotype, being slight in appearance with a BMI of 19.9 kg/m^2 and little palpable subcutaneous fat (Table 1), but with no visible veins, suggesting the presence of at least a minimal amount of subcutaneous fat. Individual I:2 was seen from his family photographs to have had a lean body habitus and had been described in hospital medical notes to be of an athletic appearance. He presented with his first myocardial infarction aged 46 and died from a subsequent myocardial infarction 10 years later. He was not known to be hyperlipidaemic, and his hospital notes revealed the results of only two random serum glucose estimations, both within the normal range. All except one (II:6) of the affected individuals had acanthosis nigricans in the axillae, and in four cases, also in the inguinal region and posterior aspect of the neck. All had clearly visible veins on their legs and arms and all except one (II:6) appeared to have a degree of muscular hypertrophy beyond that which might be expected to be perceived due simply to absence of overlying fat. Individual III:3 showed none of these features and a sum of skinfolds in the 30th centile, whereas individual II:6 had clearly visible limb veins and extremely low skin thickness measurements. No cutaneous manifestations of abnormalities of lipid metabolism were present in any of the individuals. Only one of the females had symptoms and signs to suggest polycystic ovarian disease (acne, facial hirsutism and oligomenorrhoea) whilst two of the other females underwent laparoscopic procedures during the course of the study and were seen to have macroscopically normal ovaries.

Psychological problems

All of the affected females admitted to having had difficulty coming to terms with their appearance. The males, in contrast, viewed themselves simply to be fit and strong and appeared to have remained untroubled by their lipodystrophic appearance. The women timed the onset of their own lipodystrophy around the early teenage years whereas their parents, where available to interview, considered the onset to be earlier in childhood. Affected females felt less

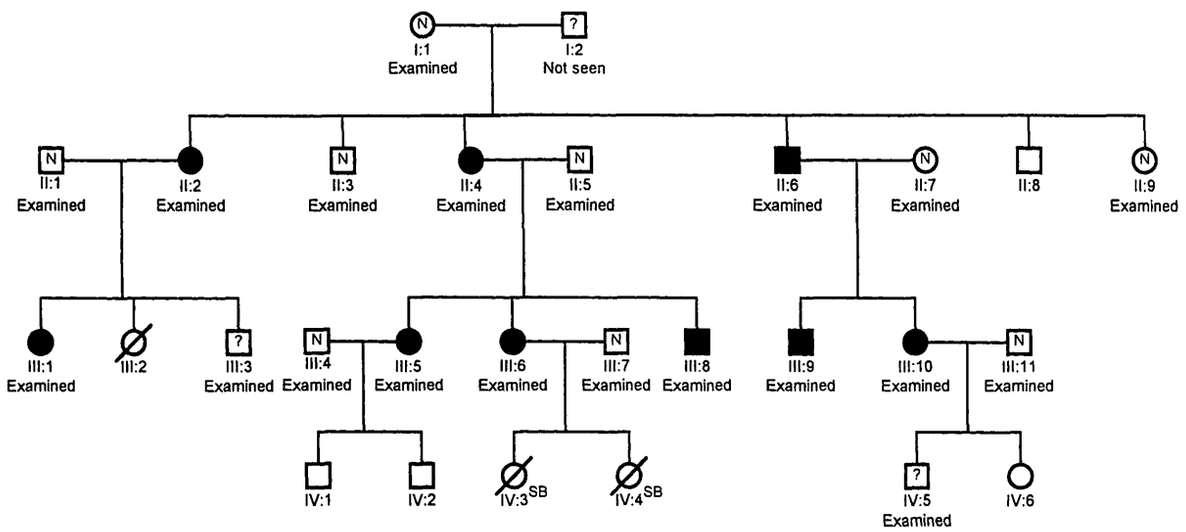

Figure 1. Family of 23 individuals. ●/■, affected phenotype; N, normal phenotype; ?, indeterminate phenotype; SB, stillborn.

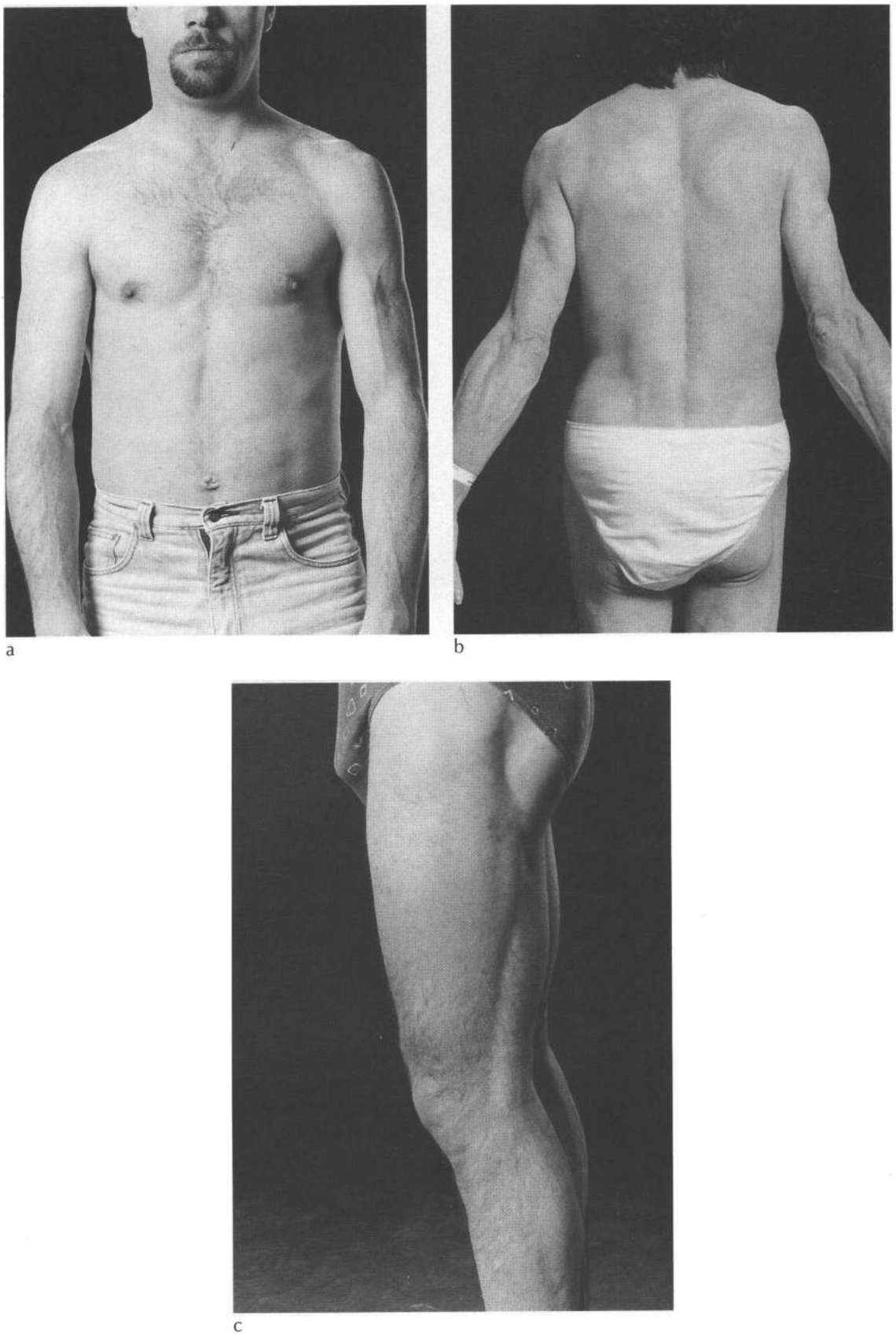

Figure 2. a,b,c Clinical photographs demonstrating lack of subcutaneous fat, sparing of the face, visible veins on the limbs and muscular hypertrophy.

Table 1 Auxological data

Pedigree	BMI (kg/m^2)	Waist : hip ratio	Mid arm circumference (cm) (centile)	Triceps skinfold (mm) (centile)	Sum of skinfolds (mm) (centile)
II : 2	23.7	0.87	23.5 (70)	4.1 (<3)	23.3 (5)
II : 4	23.1	1.0	25 (85)	4.2 (<3)	27.3 (15)
II : 6	17.8	0.88	24 (15)	3.0 (<3)	13.6 (<5)
III : 1	20.2	0.84	23 (85)	4.1 (<3)	28.5 (30)
III : 3	20	0.98	24 (15)	3.6 (<3)	19.4 (30)
III : 5	27.5	0.90	25.8 (95)	4.7 (<3)	24.8 (20)
III : 6	26	0.81	27 (>95)	4.5 (<3)	23.9 (5)
III : 8	22.2	0.85	25 (70)	5.0 (<3)	24.8 (20)
III : 9	26.1	0.91	31.5 (95)	4.7 (5)	17.7 (5)
III : 10	24.8	0.88	27.5 (95)	3.9 (<3)	20.8 (<5)

Pedigree number refers to Figure 1. BMI, body mass index (weight kg/(height m)^2). Centile information obtained from reference 15. Sum of skinfolds refers to sum of triceps, biceps, subscapular and suprailiac skinfold thicknesses.

feminine and less attractive than those around them, leading to problems with formation of relationships in the adolescent years. They would seldom wear clothing that exposed their arms or legs and had been fearful of undressing in the presence of school friends. Three of the women in their late teens and early twenties had considered liposuction of the neck and throat area. Two underwent the procedure but with such poor results, the third refused the offer of surgical intervention. One of these women has also sought the help of a psychotherapist. The attitudes of doctors in general towards their problems came under criticism. Doctors were said to have a tendency to either blame 'the lipodystrophy' for any minor physical complaint or to refuse to acknowledge its existence. Parents were also criticized for their tendency to trivialize the feelings of social isolation, something which the female lipodystrophic parents themselves admit to having felt when they had been young. Most of the women admitted to few problems currently except for the need for long sleeves and long skirts, although the desire to have only male offspring was strongly held, because they did not wish their own children to undergo their experience.

Auxology

Auxological evaluation is shown in Table 1. Skinfold thickness in triceps area and the sum of biceps, triceps, subscapular and suprailiac skinfolds are of particular note, as normal ranges are available in the literature.[15] All of the lipodystrophic individuals have triceps skinfold thicknesses on or below the 5th centile when compared with age- and sex-matched normals. The sum of skinfolds, in contrast, varies from below the 5th to the 30th centile, individual III : 3 being at this upper range. The males II : 6 and III : 9 in particular have triceps skinfolds and sum of skinfolds in the 5th or lower centiles. The waist:hip ratio is notably high in this form of lipodystrophy and the body mass index is either in the lean or overweight range. When compared with age- and sex-matched controls,[15] the mid arm circumference is at the 15th centile for II : 6 and III : 3 and at or above the 70th centile for the other affected individuals.

Cross-sectional imaging

Both male and female patients had a total lack of subcutaneous fat in all areas except the cheeks, palms and soles (Figure 3). All other areas, including the orbits, bone marrow, intrathoracic and intra-abdominal regions were shown to contain fat. Intermuscular fat was also present. The clinical impression of axial skeletal muscle hypertrophy in our kindred was confirmed by these studies.

Biochemical data

Three of the subjects had diabetic glucose tolerance tests by WHO criteria. One (II : 2) has required insulin therapy ever since the initial diagnosis 18 years ago (and currently takes a total of 86 units with resultant good control as estimated by HbA_1). One (II : 4) is treated by diet alone, and the other (III : 5) is currently taking oral hypoglycaemics with poor metabolic control, and for whom insulin therapy is being considered. Insulin resistance can be defined as the presence of elevated fasting insulin levels[16] or an elevated insulin:glucose ratio in the fasting state. The fasting insulin:glucose ratios are presented in Table 2, and were grossly elevated in all but III : 3 in whom it was normal,[17] suggesting that the insulin sensitivity of individual III : 3 is within the normal range, while his clinically lipodystrophic relatives have suppressed sensitivity to the glucose-lowering effects of insulin. The non-esterified fatty acid data, when compared with results from normal subjects undergoing the same experimental protocol, demon-

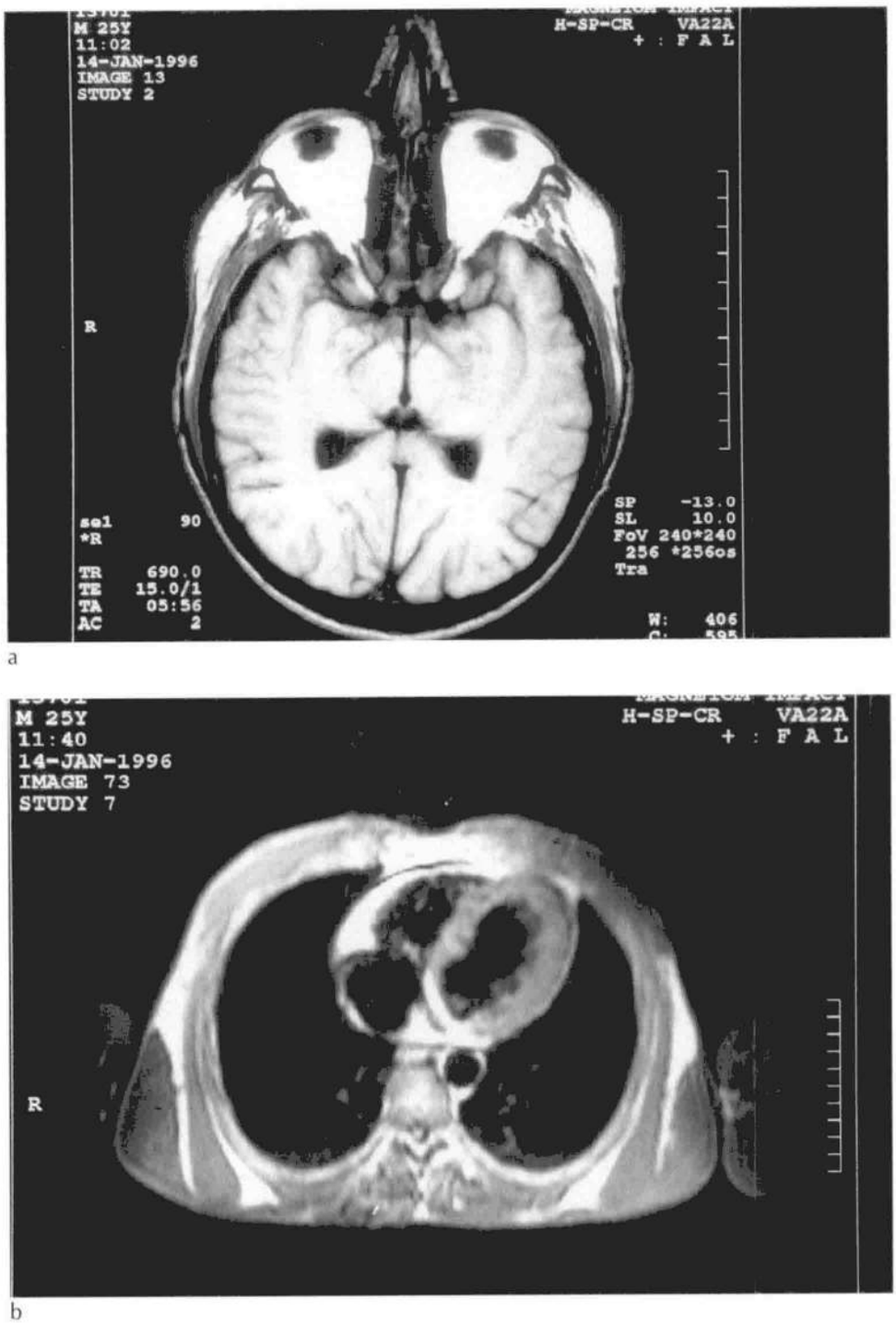

Figure 3. Axial T1-weighted MRI images of the **a** head, **b** thorax and **c** abdomen. Fat appears white. There is an absence of subcutaneous fat, whereas in other areas such as the orbits, mediastinum and intra-abdominal cavity, fat is clearly present.

strates some variability within the phenotype (N.J. Wareham, personal communication).[18] Excluding III:3, seven individuals failed to suppress serum NEFA to the level achieved by individuals matched for sex and glucose tolerance, and as can be seen from the table, the absolute values of serum NEFA show wide variation. In contrast, patient III:8 had a low fasting NEFA and succeeded in suppressing this further. Patient III:3 suppressed to a level just above the expected range. Serum triglyceride was elevated above 1.0 mmol/l in six patients and above 2.0 mmol/l in only one patient, the woman with insulin-treated diabetes.

Discussion

We present for the first time a detailed description of a kindred with unequivocal evidence of autosomal

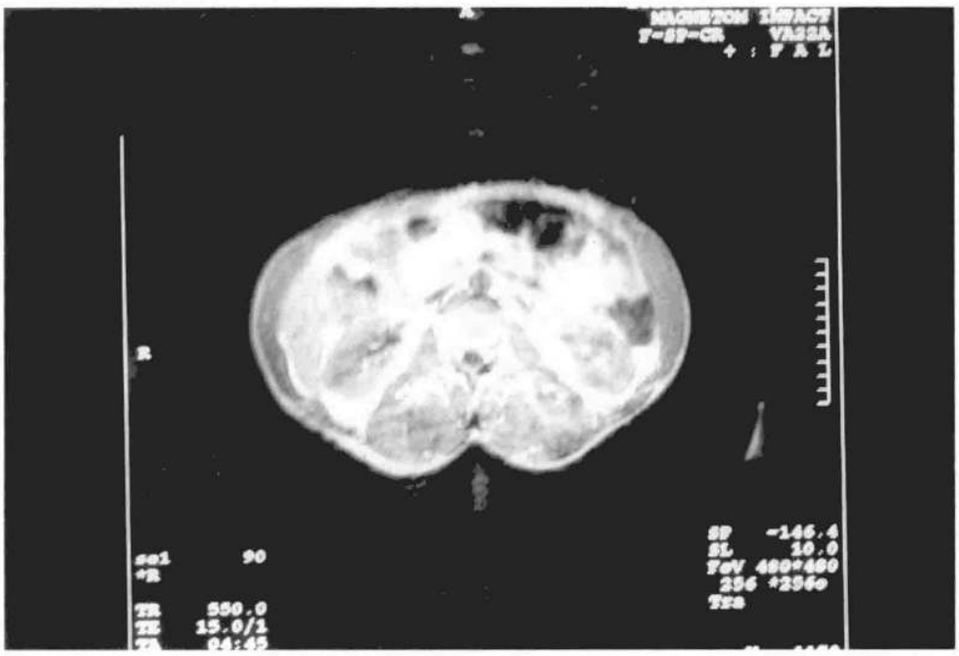

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Table 2 Biochemical data

Individual	Time (min)	Glucose (mM)	Triglyceride (mM)	NEFA (mM)	Insulin (pM)	Fasting insulin/glucose	Intact proinsulin (pM)	32-33 split proinsulin (pM)
II:2	0	25.2	2.2	1556	NA	NA	NA	NA
	60	37.1		1396				
	120	43.5						
II:4	0	6	3.5	694	146	24.3	26	26
	60	11.1		438	1470		96	108
	120	12.5		161	2307		276	200
III:1	0	5.1	1	483	105	20.6	3.2	7.2
	60	7.1		124	1198		19	49
	120	7.5		75	695		26	59
III:3	0	4.6	1.3	242	33	7.1	2.9	4.9
	60				NA		NA	NA
	120	4.7		72	166		21	28
III:5	0	17.8	2	315	408	22.9	202	205
	60	24		185	882		300	231
	120	20.5		165	778		307	233
III:6	0	4.9	1.2	618	201	41	7	16
	60	8.5		244	3232		30	94
	120	4.8		1410	2254		42	115
III:8	0	5.3	0.9	287	148	28	8.4	17
	60	8.5		91	985		37	92
	120	4.8		98	72		18	30
III:9	0	5.5	1.9	454	87	15.8	4.6	3.6
	60	9.3		153	445		16	19
	120	5.5		145	172		9.1	9.1
III:10	0	5.6	0.8	178	99	17.7	7	11
	60	10.1		99	1466		23	50
	120	2.1		27	206		15	24

Serum cholesterol results are not tabulated and ranged from 3.9 to 8.1 mmol/l. NA, not available.

dominant transmission of a form of face-sparing lipodystrophy. The previous postulate of X-linked dominance with lethality in the hemizygous male[2,3] may either reflect incomplete ascertainment owing to difficulties in assigning affected status to the male, or genetic heterogeneity for the Dunnigan-Kobberling phenotype. The general importance of this syndrome lies in its associated metabolic abnormalities and the presence of central intracavity adipose tissue in the absence of peripheral adipose tissue. There is overwhelming evidence that many common diseases such as non-insulin-dependent diabetes mellitus,[19] obesity,[20] hypertension,[21] polycystic ovary disease,[22] dyslipidaemia[23] and atherosclerosis[24] are associated with varying degrees of insulin resistance. Many of these diseases tend to cluster together in individuals with an increased risk of ischaemic heart disease.[25] Moreover, a central pattern of deposition of fat in human obesity is associated with increased risk of ischaemic heart disease independent of total body fat.[26] Molecular genetic disease-gene mapping presupposes the elucidation of its mode of inheritance. The demonstration of autosomal dominant segregation in this kindred will facilitate further investigation by genetic linkage analysis. The eventual identification and characterization of the disease gene should provide further insight into mechanisms of insulin resistance and factors leading to differential deposition of fat.

The individuals in this pedigree appear to suffer from a more 'benign' form of face-sparing lipodystrophy than those previously described by Dunnigan and Kobberling. In particular, diabetes was detected in over half of these latter cases as were severe degrees of hyperlipidaemia leading to cutaneous xanthomas (Table 3). It is possible, therefore, that the present pedigree demonstrates a condition distinct from Dunnigan-Kobberling syndrome. Table 3 compares features of the present kindred with those previously described. The only consistent findings are the pattern of lipodystrophy and the presence of hyperinsulinaemia.

Detailed metabolic assessment of this pedigree has identified further complexity in the underlying biochemical defect. Stimulated insulin levels in individuals with normal glucose tolerance display a wide variation despite a presumed common basic metabolic abnormality. Insulin sensitivity is dependent upon the interaction (epistasis) of a number of genetic determinants which may modulate the impact of a single gene defect elsewhere in the biochemical pathway. In addition to the resistance to glucose uptake, most patients display a subnormal response of serum NEFA to glucose loading, with a wide variation in degree of suppression achieved. In non-insulin-dependent diabetes (NIDDM) and impaired glucose tolerance, the fasting NEFAs are elevated above the levels found in non-lipodystrophics but are suppressed more effectively after glucose than in our patients.[18] *In vivo*, the decrease in NEFA after oral glucose is secondary to the suppressive effect of insulin on adipocyte lipolysis. The subnormal suppression of NEFA in our lipodystrophic patients, with apparently normal volumes of intra-abdominal fat but much decreased levels of subcutaneous fat, raises the possibility that the subcutaneous adipocytes may exhibit atypically high metabolic activity consequent upon the inadequate suppression of lipolysis

Table 3 A comparison of the features demonstrated in previous reports and the present pedigree

Feature	This pedigree	Davidson *et al.*, 1975	Kobberling *et al.*, 1975	Burn & Baraitser, 1986	Dunnigan *et al.*, 1974
n	22	8	5	4	2 pedigrees, 6 & 6
Face-sparing lipodystrophy	+	+	+	+	+
Diabetes*	3/8	7/8	3/5	2/4	1/6 & 3/6
Hyperlipidaemia**	1/8 mild	2/3 mild to moderate	5/5 to varying degrees	4/4 to varying degrees	3/4 to varying degrees
Xanthomata	No	No	2/5	2/4	2/4
Hypertension	No	2/3	?	1/4	Yes, in one of two pedigrees
Hirsutism	+/−	+/−	+/−	?1/3	No
Acanthosis nigricans	+	+	+	1/4	+

* Lipodystrophics with/total lipodystrophics. ** Triglyceride >2 mmol/l.

by insulin. This may result in very small subcutaneous adipocytes and a high and poorly suppressed serum NEFA. Increased availability of free fatty acids would be expected to exacerbate the insulin-resistant state in skeletal muscle secondary to substrate competition[27] and stimulation of gluconeogenesis in the liver.

The muscular hypertrophy seen in our patients may be due to an effect of the high prevailing insulin on protein synthesis. Insulin could exert its action on protein synthesis by binding to its own receptor and activating a post-receptor pathway distinct from those involved in its other actions or it could act via the IGF-1 receptor. It is unlikely to be due to intramuscular triglyceride deposition, as this should have been visible on the MRI images.

The underlying molecular mechanisms leading to any of the forms of lipodystrophy are presently unknown. However, a number of genetic defects associated with severe insulin resistance have been elucidated in man. Homozygous mutations of the insulin receptor have been reported in both leprechaunism, in which there is also a paucity of adipose tissue, and some cases of type A syndrome of insulin resistance. Mutations in the insulin receptor have been excluded as a cause of Dunnigan-Kobberling syndrome using studies involving single-stranded conformational polymorphism (SSCP).[28]

Candidate genes for lipodystrophy include GLUT 4, the insulin-dependent glucose transporter present in adipose and muscle tissue. It has been excluded as a major gene in the causation of NIDDM,[29] but GLUT 4 'knockout' mice are insulin resistant and have much reduced adipose tissue.[30] In addition to defects in the pathways of fat metabolism, disruption of the control of transcription in adipocytes by transcription factors may also be implicated in the pathogenesis of lipodystrophy. Peroxisome proliferator activator receptor γ (PPARG)[31] and C\EBP$\alpha$[32] are transcription factors which interact with the promoters of a number of adipocyte genes and are known to be important in differentiation of preadipocytes into adipocytes.

In summary, we have described an extended pedigree with autosomal dominant transmission of face-sparing lipodystrophy of the Dunnigan-Kobberling type. In addition to the biochemical evidence of insulin resistance and abnormal NEFA metabolism, we have emphasized the psychological impact of the disorder. Possible aetiologies are discussed, as is the relevance of this rare condition to common disorders conferring considerable morbidity and mortality in the Western world.

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