GENERALISED LIPODYSTROPHY

K E Choo, A Sharifah, W A Ariffin, M Mafauzy

ABSTRACT

We report a Malay girl suffering from generalised lipodystrophy, with clinical features of absence of body adipose tissue, hepatomegaly, hyperpigmentation and muscular hypertrophy. She also had hyperlipaemia, hypercholesterolemia and non-ketotic insulin-resistant diabetes mellitus. The possibility of malnutrition-related diabetes mellitus was excluded because of (a) no personal or family history of malnutrition (b) no pancreatic calcification (c) total loss of subcutaneous fat and (d) her requirement for insulin was more than 21.2 units/kg body weight which would be too high even for malnutrition-related diabetes mellitus. Attempts were made to control her diabetes initially with subcutaneous boluses insulin, then continuous intravenous insulin infusion (CIVII) and finally orally with fenfluramine and chlorpropamide.

Keywords: Lipodystrophy, non-ketotic insulin-resistant diabetes, CIVII.

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INTRODUCTION

The complex syndrome of lipodystrophy first described by Lawrence in 1946 (1) is characterised by complete absence of body adipose tissue, hepatomegaly, hyperlipaemia, insulin-resistant diabetes without ketoacidosis, hypermetabolism, accelerated growth and maturation, hirsutism, hyperpigmentation and muscular overdevelopment. Over 80 cases have been reported in the world literature (2). We report here a Malay girl with generalised lipodystrophy.

CASE REPORT

A. was a product of non-consanguinous marriage. She had 5 other normal siblings (4 boys and 1 girl). At the age of 4 years she was seen at the General Hospital Kota Bharu (GHKB) with a history of lethargy, polydipsia and loss of weight. At 8 years old she was readmitted to the GHKB with complaints of premature ageing of the face (Fig. 1) and was treated with insulin injections and an oral hypoglycaemic. However, her parents discharged her from hospital against medical advice after three months stay and did not bring her for follow-up visits.

Three years later, she was admitted to the Hospital Universiti Sains Malaysia. In this admission, on questioning it was determined that her diet at home consisted of plenty of rice mixed with fish and vegetables consumed thrice a day. She took little meat and no cassava. Examination showed a dark looking and cachectic girl (Fig 2). She weighed 17kg (< 3rd percentile), height was 128cm (3rd - 10 percentile), blood pressure was 120/80 and heart rate was 80/min. Her face resembled an old lady's. She had generalised loss of subcutaneous fat, prominent veins and bony structures. Her trunk and limbs were muscular. She had fungal infections of the skin and nails. The knees and elbows revealed multiple xanthomata (Fig 3). She had bilateral

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Fig 1
Girl with generalised lipodystrophy at 8 years old

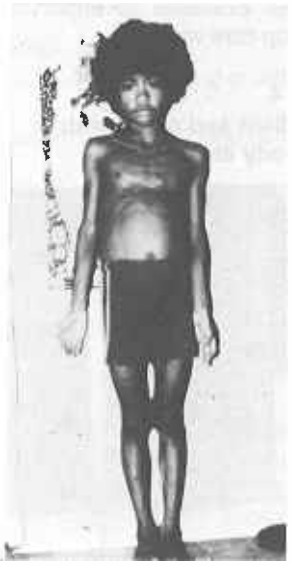
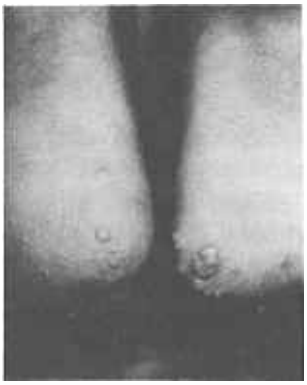


Fig 2
Girl with generalised lipodystrophy at 11 years old

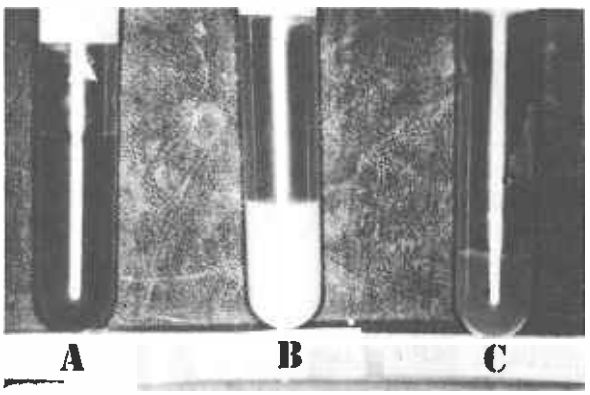
Fig 3
Elbows showing xanthomata in girl with generalised lipodystrophy.



posterior subcapsular cataracts in the eyes. Her fundi demonstrated normal optic discs but grade IV atherosclerotic blood vessels. Her intelligence quotient was 80-90.

The blood and urine investigations are shown in Table I. The skull-xray, chest-xray, plain abdominal-xray, ultrasound studies of the abdomen, computerised tomographic scan of the brain, electroencephalogram, electrocardiogram and echocardiogram were normal. Electromyogram studies reported denervation changes. Biopsy over the knee confirmed it was xanthoma. Her skeletal age was estimated to be between 7 years 10 months and 8 years 10 months. Hyperlipaemia, hypercholesterolaemia and turbidity of the serum (Fig. 4) became normal once treatment of her diabetes mellitus had been instituted. Initially she was managed with 8-hourly subcutaneous injections of insulin plus diabetic diet. However, since this method could not control her diabetes she was started on continuous intravenous insulin infusion (CIVII), beginning at 2 units per hour and increasing to 15 units per hour. She was also treated with 8-hourly boluses of intravenous insulin (28 units) just before meals plus free diet. Six days after starting CIVII she developed thrombophlebitis. On the ninth day of CIVII she had septicaemia (Acinetobacter). She did not at anytime develop ketosis. Finally CIVII regime was abandoned after 20 days because (a) of fear of recurrent septicaemia, (b) she could not give injections herself owing to poor eyesight, (c) none of her family members were willing to learn and give insulin injections to her and (d) no health staff was available to supervise injections and provide follow-up care at home.

Fig 4
Serum of a normal patient and of girl with generalised lipody strophy.



After recovery from septicaemia she was started on fenfluramine (20mg tds) with chlorpropamide (125mg o.m.). However, before her diabetes could be stabilised, her parents requested her discharge since she had already stayed two months in hospital. Two months later, at the outpatient clinic, she appeared thinner, was not ketotic, and her random blood sugar was 26.4mmol/L. Further evaluation as to whether she responded to fenfluramine and chlorpropamide could not be made because she never turned up again.

Table I

Laboratory Findings Of Child With Generalised Lipodystrophy

Tests	Patient	Normal Values
Serum Cholesterol	29.1mmol/L	3.4-6.5mmol/L
Serum Triglycerides	24.01mmol/L	0.5-2.2mmol/L
Creatine Phosphokinase	32IU/L	5-50IU/L
Compliment 3 (C3)	0.9gm/L	0.6-1.30gm/L
Compliment 4 (C4)	0.439gm/L	0.2-0.6gm/L
Serum Amylase	39IU/L	114-342IU/L
HbAIC	10%	6-8.3% (> 10% poor control)
Para Amino Benzoic Acid Excretion (PABA)	14%	>40%
Serum Insulin	Random 0.24ng/ml	0.2-1.3ng/ml
C-peptide	Random 0.45pmol/ml	0.18-0.63pmol/ml
Glucagon test (i.v. glucagon 1mg)		
0 min	0.17pmol/ml	Flat response
5 min	0.16pmol	
10 min	0.14pmol/ml	
20 min	0.13pmol/ml	
30 min	0.12pmol/ml	
Glycosylated Fructosamine	3.44mmol/L	2.0-2.8mmol/L
Growth hormone (GH)	2.5ng/ml	≤7ng/ml
Thyroid stimulating hormone (TSH)	1.3IU/ml	≤7IU/ml
Thyroxine (T4)	100nmol/L	64-167nmol/L
Tri-Iodothyronine (T3)	1.3nmol/L	1.2-3.4nmol/L
Testosterone	0.1nmol/L	0.5-3.8nmol/L
24 hours urine pregnanetriol	0.3umol/day	0-22umol/day
17 oxogenic steroids	10umol/day	1.7-8.7umol/day
17 oxosteroids	14umol/day	8.7-45umol/day
Liver function tests (LFT)		
Total protein	96gm/L	55-82gm/L
Albumin	44gm/L	37-50gm/L
Globulin	42gm/L	18-32gm/L
AST	32IU/L	5-70IU/L
ALT	22IU/L	5-50IU/L
ALP	20IU/L	70-140IU/L
S. Bilirubin	16mmol/L	< 20mmol/L
Blood urea	2.9mmol/L	3.2-6.7mmol/l
Serum electrolytes		
Sodium	130mmol/L	135-148mmol/L
Potassium	3.7mmol/L	3.5-5.0mmol/L
Serum calcium	2.26mmol/L	2.15-2.65mmol/L
Chromosomal studies	normal	
Urinalysis	normal	

DISCUSSION

Generalised lipodystrophy occurs in congenital (autosomal recessive) and acquired forms (3,4). In both types there is a preponderance of female. Parental consanguinity (3-6) and cases affecting more than 1 sibling in the same family (4,7-9) have been described. The aetiology of lipodystrophy is still obscure. Oseid et al have demonstrated decreased binding of insulin to its receptors in patients with congenital lipodystrophy (10). Seip (4) had likened it to a diencephalic syndrome involving the hypothalamus and probably resulting from trauma and infections. Louis and coworkers have isolated a polypeptide exhibiting adipokinetic, diabetogenic and antiinsulin properties (11). Yet others like Zarafonetis (12) and Rudman (13) had isolated lipid mobilising subtances from the anterior pituitary gland.

Insulin-resistant diabetes without ketosis seen in our case is a common association with lipodystrophy although Robbins (14) and Aharon (15) have reported ketoacidosis in their cases. Hypertension and hypocomplimentaemia described by Surjit Singh in his patient (2) are uncommon (5, 16, 17). Skeletal muscle hypertrophy is due to the loss of subcutaneous fat and true muscle hypertrophy (2). Muscle biopsies have shown normal myofibrils separated by excess of fat droplets and glycogen (18). Muscle enzymes were elevated in one report (2). Cataracts are uncommon although seen in our case. As opposed to most reports (1, 16, 19) including ours one isolated case had a raised triiodthyronine (T3) and low thyroxine (T4) (2). Most workers have also found normal follicular stimulating hormone (FSH) and leutinizing hormone (LH). The majority of reported patients had increased bone age (19,20) unlike our case.

Similarly, unlike us, others have reported widening of basal cistern and third ventricle (1, 6) and increased pneumatization of sinuses and mastoids (2, 19). There have been reports of cardiomegaly with septal hypertrophy on echocardiography (20) but these were absent in our case. She had low PABA excretion and poor C-peptide response to intravenous glucagon suggesting both pancreatic exocrine and endocrine deficiencies. The possibility of malnutrition-related diabetes mellitus (MRDM) was considered. However, there were a few points not in favour of the diagnosis. (a) There was no history of malnutrition in her and the rest of the family members were well nourished. (b) There was no pancreatic calcification both on Xray and on ultrasound examination. (c) There was total loss of subcutaneous tissue which would be unusual even for severe malnutrition. (d) Her requirements for insulin was more than 21.2 units/kg body weight which would be too high even for MRDM. Furthermore, the concept of malnutrition causing diabetes mellitus, especially of the non-calcific pancreatic type (protein deficient diabetes mellitus) has been questioned (21).

Currently there is no effective treatment of lipodystrophy. Based on Leblanc's use of subcutaneous insulin injections (22), Aharon et al (15) have demonstrated a way of controlling diabetes and other metabolic abnormalities in congenital lipodystrophy by employing CIVII. Like us they also experienced problems of sepsis. Trystad reported fenfluramine improved carbohydrate tolerance in congenital lipodystrophy (23, 24) although Wilson could not confirm this finding (25). Corbin (26) had reported success in treatment of one patient with pimozide. It is hoped that further studies together with follow-up of patients suffering from lipodystrophy will enable better understanding and management in the future.

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ERRATUM

NEONATOLOGY IN SINGAPORE by K. W. Tan (Singapore Med J 1990; 31: 63 - 68)
Table VI should be read as follows:

Table VI
BED AND STAFF REQUIREMENTS FOR NEONATAL INTENSIVE CARE AT NATIONAL LEVEL – CURRENT AND EXPECTED

Hospital	Level 1 Beds	Level 2 Beds	Level 3 Beds	Doctors		Nurses for L3 beds	
				Neonato-logists	Others	Staff Nurses	Others
TPH		20	5	1	4	7	4
KKMH		34	6	2	8	10	10
AH		25	6	1	5	11	7
SGH		19	6	1	6	8	7
NUH		15	5	2	3	23 (L2 and L3)	5
5 major private hospitals		20	3	No dedicated Level III Neonatal Intensive Care Unit			
Total		133	31	7	26	59	33
Total Expected (based on 40.000 deliveries per year)		280	40				