Acta Dermatovener (Stockholm) 52: 379–385, 1972

PSEUDOSCLERODERMA CONCOMITANT WITH A MUSCULAR GLYCOGENOSIS OF UNKNOWN ENZYMATIC DEFECT

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Abstract. Scleroderma-like skin lesions are described with involvement of the muscles of the extremities in two cases of muscular glycogen storage disease.

Biochemical, histochemical and electronmicroscopic data are reported. The glycogen level in the muscles was 4.78% in one case and 2.4% in the second. Since no enzymatic defect was detected in glycogen degradation, the cases cannot be classified into any of the known types of glycogenosis. Some findings appeared to indicate a concomitant derangement of tryptophan metabolism and retarded intestinal absorption.

Some cases of phenylketonuria (PKU) with concomitant scleroderma-like lesions of the skin and muscles have been reported (1, 2, 6, 14, 16, 29).

In our cases of PKU with skin and muscles indurations, we were able to demonstrate derangements of phenylalanine as well as tryptophan metabolism (14, 29) similar to those found by Drummond et al. (6) in their case of PKU with scleroderma-like changes.

The present paper deals with 2 cases of pseudoscleroderma of a similar clinical type but without PKU, with concomitant mental retardation in one case and normal mental development in the second. Both patients showed the features typical of glycogen storage disease of the muscular type but no enzymatic defect could be established.

Since the indurations of the skin and muscles resembled the scleroderma-like lesions in PKU, we investigated possible role of phenylalanine and tryptophan metabolism in the pathogenesis.

CASE REPORTS

Case 1

J. K., a 19-year-old male (Fig. 1); parents unrelated and healthy; younger sister healthy. The mother suffered four spontaneous abortions before the boy's birth. Although at term, the delivery was difficult and protracted, and the baby was in a state of slight asphyxia; he was very emaciated and fed poorly. The physical and psychomotor development was retarded. The disease started in the fourth month and the boy has been under our observation since the eighth year of life for more than 10 years.

Skin and muscle changes. Skin lesions consisted of indurations and atrophy of the skin, most pronounced in the lower extremities. The skin was taut and bound down. Contractures were more pronounced in the lower extremities. The muscles of the trunk, especially in the lumbar region, and in the buttocks and thighs, were visibly hardened.

Neurological examination revealed no changes. The mental disturbances were of the debilitas type.

Inner organs: no abnormalities.

Electrocardiogram, electroencephalography, and X-rays of the chest, digestive tract, and skeleton were normal.

Electromyography revealed slight to moderate primary myogenic involvement.

Routine analysis failed to reveal any abnormalities in the blood count; slight hypogammaglobulinemia (15.2%); liver function tests, levels of electrolytes, cholesterol, urea, creatine and creatinine were normal.

Serum aldolase, aspartic transaminase (SGOT), and alanine transaminase (SGPT) were normal, and creatine kinase was slightly elevated (5 units).

Histology of quadriceps of thigh ($H+E$). Muscle fibres were atrophic, with no sign of degeneration. No inflammatory infiltrates were found in the widened interstitial spaces. PAS-reaction (Fig. 2), Best's carmine and mucicarmine staining were strongly positive. After treatment with 1% diastase (BDH), PAS-staining became negative.

Histoenzymatic studies of muscles. Phosphorylase activity was maintained, though somewhat reduced. Oxidative enzymes, ATP-ase and unspecific esterases were normal.

Electron microscopy of muscles. The changes involved a reduction of actin as well as myosin filaments in sarcomeres. They were particularly pronounced in the neighbourhood of the sarcolemma, which was chiefly affected, whereas the central parts of the muscle fibres were less changed. "Z" bands were relatively well preserved. The interfibrillary spaces were considerably wider (Fig. 3 *a*). They contained glycogen granules which varied in number

Fig. 1. Case 1.

between different cells, and resembled the patterns seen in the glycogen storage disease (Fig. 3 *b*). The mitochondria were unchanged. There were numerous structures corresponding to lysosomes containing a dense granular material with vacuoles.

Case 2

J. G., a man aged 29 years (Fig. 4); parents unrelated; delivery normal. Indurations had been noted at the age of 6–7 months. The contractures developed gradually. The disease was diagnosed as scleroderma and treated for several years.

Skin and muscle changes. The muscles were hard and tight, especially in the proximal parts of the extremities, especially in the lower ones. Movement in the shoulder and pelvic girdles was limited and contractures were more pronounced in the lower extremities. It is worth noting that the muscles of the shoulder girdle were well developed, but hard. Skin indurations and atrophies were present in the proximal parts of the extremities; the skin seemed to be bound fast to the underlying structures; the chest was stiff which was a severe handicap for the pa-

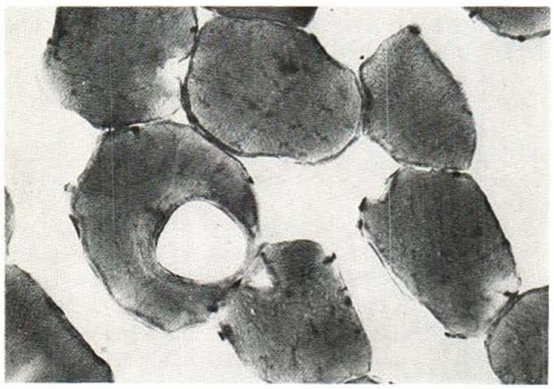

Fig. 2. Case 1. Muscle histology. PAS-staining, × 300.

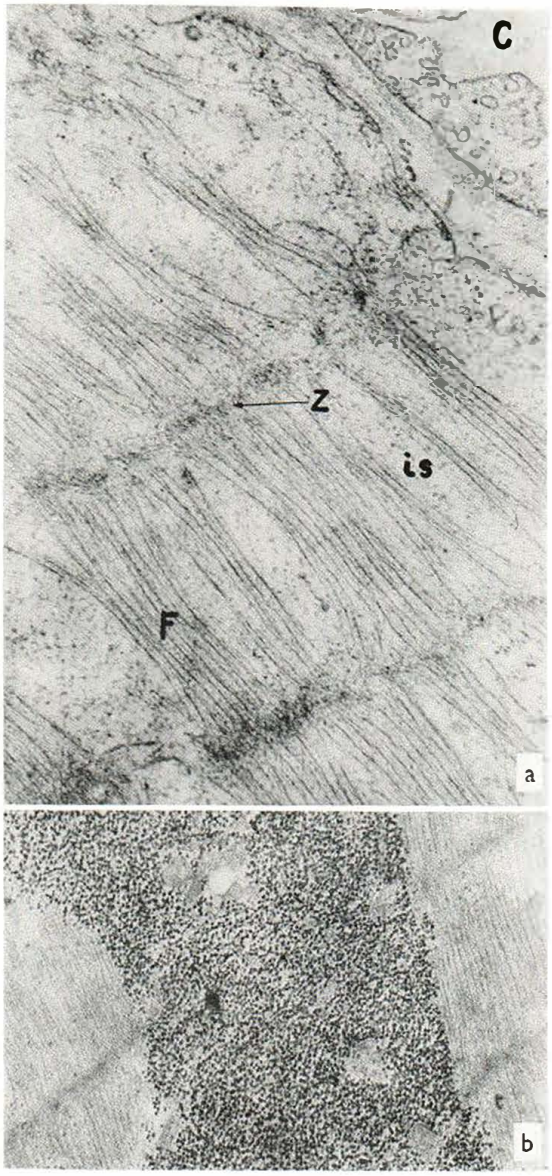

Fig. 3. Electron microscopic pictures (case 1). (*a*) Interfibrillary spaces (*is*) enlarged; the number of filaments (*F*) in sarcomeres is reduced. "Z" bands (*Z*) are preserved. In the right upper corner part of a capillary (*C*) is visible. × 28 800. (*b*) The interfibrillary space is enlarged, tightly packed with glycogen granules. × 33 600.

tient. The skin and underlying muscles of the quadriceps group were mostly affected. Facial skin was not hard, though rather taut, with some smoothing of the lines of expression but without atrophy of lips. The skin of the hands and feet was normal.

Electrocardiogram: Syndrome Wolf-Parkinson-White (type B).

Roentgenograms of the chest, digestive tract and bones were normal.

Electromyography: individual polyphasis potentials.

Routine analysis: Erythrocytes, 3.59 mil.; hypogammaglobulinemia (13.6%), liver function tests normal, as also were the levels of cholesterol, urea and creatinine in the serum. Creatine in the urine, 137 mg/24 h (normal—up to 50 mg/24 h).

Serum aldolase, aspartic transaminase (SGOT) and alanine transaminase (SGPT) were normal; creatine kinase, normal. Waaler-Rose was considerably elevated (320 u.).

Histology of skin: Epidermis and corium were markedly atrophic. Connective tissue stroma was loose, somewhat oedematous. Appendages were reduced in number. There were no inflammatory infiltrates. Number of elastic fibres was reduced.

Histology of muscles: Muscle fibres showed pronounced atrophy without degeneration. PAS-staining was strongly positive, becoming negative after diastase treatment.

Histoenzymatic studies: Phosphorylase activity, oxidative enzymes, and unspecific esterases were normal.

Electron microscopy of muscles: an accumulation of glycogen was found in the markedly dilated interfibrillar spaces. The changes were similar to those in case 1.

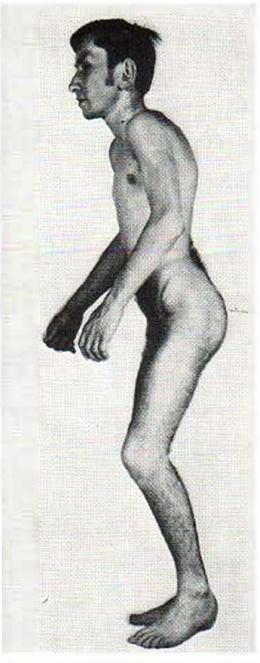

Fig. 4. Case 2.

BIOCHEMICAL STUDIES

Methods

A. *Glycogen in muscles and erythrocytes*

Glycogen in muscles (quadriceps femoris extracted according to Hassid et al. (10), was determined by the method of Seifter et al. (27). Its structure was established by absorption spectrophotometry of its complex with iodine according to the method of Krisman (17). Erythrocyte glycogen was determined by the method of Sidbury et al. (28).

B. *Enzyme assays of muscles*

(*a*) Acid maltase (alpha-1,4-glucosidase) and phosphorylase were determined by the method of Hers (11).

(*b*) Phosphohexoisomerase was determined by the method of Bodansky (4); 10% extracts of muscle were diluted with water 1 : 1 000.

(*c*) Phosphoglucomutase was determined by the method of Bodansky (5) devised for serum, except that the incubation period was cut to 90 min.

C. *Ischemic exercise*

The serum lactic acid curve after ischemic exercise was determined according to the method of Thomson et al. (34) and serum lactic acid according to the method of Strom (31).

D. *Tolerance tests*

(*a*) *Phenylalanine* (*case 1*). After a load of 0.1 g of l-phenylalanine per kg of body weight, the levels of this compound and tyrosine were determined in the blood by the method of LaDu & Michael (18).

(*b*) *D-Xylose.* After loading with 5 g D-xylose (case 1) or 12 g (case 2), xylose was determined in 5-hour urine and in the blood according to the method of Roe & Rice (25).

(*c*) *Saccharose.* After loading with 100 g saccharose (case 1) or 50 g (case 2), the glucose level in the blood was determined by the method of Nelson (22).

(*d*) *Tryptophan* (*case 2*). After loading with l-tryptophan at a dosage 0.1 g/kg body weight, the tryptophan level in the serum was determined by the method of Opienska-Blauth (23); total indoles (T.I.) and indole-acetic acid (IAA) free and bound in urine, according to the method of Fischl & Rabiah (8); indican (I.S.), by the method of Meiklejohn (21); 5-hydroxyindole-acetic acid (5-HIAA), by the method of Udenfriend et al. (35); kynurenine (K), by the method of Thompsett (33); and xanthurenic acid (XA), by the method of Weller & Fichtenbaum (36).

E. *ATP*

The blood ATP level was determined by the method of Wenclewski (37).

F. *Fructose-6-phosphate*

Fructose-6-phosphate (F-6-P) was determined by the method of Roe (24).

RESULTS

Muscle biochemistry

The results are presented in Table I. Muscle glycogen was considerably elevated in case 1 and

Table I. *Biochemical and enzyme analyses of muscles and erythrocytes*

	Case 1	Case 2	Controls (own data) 1	2	3	Controls (data from literature)
Muscle glycogen (g/100 g wet weight)	4.8	2.4	1.6	0.7	1.0	0.5–1.5
Erythrocytes glycogen μg/g of haemoglobin	30.0 60.0[a] 24.0[b]	92.0	—	—	—	20.0–100.0 (mean 57.0)
Phosphorylase (μM P/g/min)	53.0	51.8	48.7	43.0	58.3	45.0–123.0
Acid maltase (μM/g/min)	0.067	0.055	0.041	0.108	0.091	0.05–0.100
Phosphoglucomutase (μM/g/h)	2 200[c]	932	1 400	1 860	1 142	—
Phosphohexoisomerase (μM/g/h)	3 822	4 741	3 900	1 900	—	—
Fructose-6-phosphate (μM/g wet weight)	0.120	0.057	0.092	—	0.110	0.05–0.100
Serum ATP level (mg%)	1.01 0.82[a] 1.13[b]	1.16	—	—	—	1.80–2.87

[a] Mother of patient 1.
[b] Father of patient 1.
[c] Based on labile phosphorus determination.

moderately in case 2. In case 2 glycogen was also slightly elevated in erythrocytes. The structure of glycogen was normal in both cases.

Ischemic exercise

In both cases there was partial inhibition of glycogenolysis in the ischemic exercise (Fig. 5), the inhibition being more pronounced in case 1.

Tolerance tests

(a) The *phenylalanine* blood levels was normal, but the peak after loading was reached in case 1 in 3 hours as against 1 hour in the normal control. The level of phenylalanine in the blood without loading was 2.3 mg% (normal), and of tyrosine, 1.0 mg% (normal).

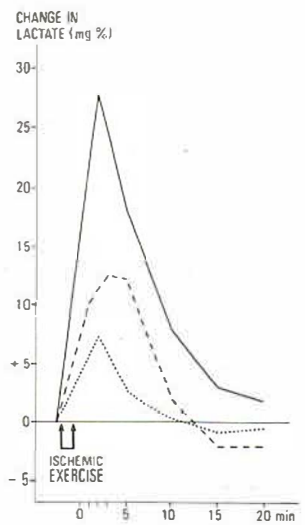

Fig. 5. Rise of blood lactic acid level after ischemic exercise. —, Control; – – –, case 1; · · ·, case 2.

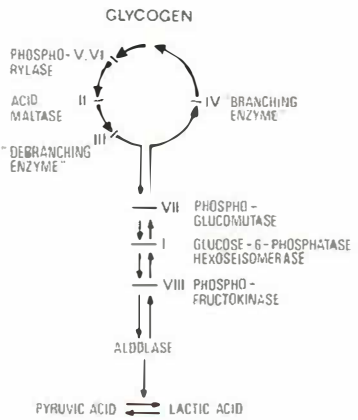

Fig. 6. Diagram (simplified) of glycogen metabolism; enzymatic defects are marked and numbered. I, von Gierke's disease. II, Pompe's disease. III, Cori's disease. IV, Amylopectinosis. V, McArdle's disease. VI, Hers disease (liver phosphorylase deficiency). VII, Phosphoglucomutase deficiency. VIII, Phosphofructokinase deficiency.

Table II

A. Before l-tryptophan loading
B. After l-tryptophan loading

	Tryptophan metabolites in urine								
	T. I. (g/24 h)	IAA free	IAA bound	IS	XA	K	5-HIAA (mg/24 h)	Nitrogen amino in urine (mg/24 h)	Tryptophan in serum (mg%)
	micromoles/kg/24 h								
Case 1	2.00	3.16	5.28	[a]	N.D.	N.D.	1.52	260	1.45
Case 2									
A	0.67	1.60	2.90	6.0	0.70	0.05	3.31	115	1.50
B	1.87	8.55	10.17	9.6	1.92	4.12	N.D	N.D.	16.80[b]
Normal adults (data from literature)									
A	up to 0.6	up to 1.6	up to 2.0	up to 8.0	up to 0.5	up to 0.5	1.0–5.0	100	0.8–1.4
B	up to 1.0	up to 5.0	up to 8.0	up to 8.5	up to 5.0	up to 13.0	—	—	18.0–20.0
			% tryptophan converted to metabolites						
Case 2			1.44	0.75	0.24	0.83			
Normal			0.24–1.30	0.60	0–1.4	0.24–3.0			

[a] In Obermayer's test.
[b] Maximum level after $1^1/_2$ hours (normal).
N.D., Not done.
T. I., Total indoles; IAA, indole-acetic acid; I.S., indican; XA, xanthurenic acid; K, kynurenine; 5-HIAA, 5-hydroxyindole-acetic acid.

(*b*) Elimination of *xylose* in urine was quantitatively normal after loading (28% in case 1, and 34% in case 2, in 5 hours), but the dynamics was slower in case 1, the maximum concentration in the blood having been reached after $2^1/_2$ hours (versus 2 hours at the most in normal elderly people).

(*c*) Blood sugar levels after *saccharose* loading showed a slow decrease in glucose during the first hour after the peak was reached.

(*d*) *Tryptophan metabolites* in urine are presented in Table II. In both cases there was a considerable increase in the level of total indoles (in case 1 even without loading) and of IAA, especially of the bound one (before load in case 1, and before and after load in case 2). In case 2 after loading there was also an abnormal increase of indican (0.75% of the tryptophan introduced was converted into indican, maximal normal level being 0.60%). Levels of xanthurenic acid and kynurenine before and after loading, and also the 5-HIAA level, were normal.

(*e*) Serum *ATP* was considerably lower in both cases as also in the parents of patient 1 (Table I).

(*f*) The level of F-6-P in the muscles was normal (Table I).

DISCUSSION

The cases described show a marked similarity to scleroderma, especially patient 2, who was diagnosed and treated for scleroderma for several years. In case 1 the muscle indurations were more pronounced in the thighs, pelvic girdle and lumbar region, and the skin in these regions was taut, somewhat hardened, and/or in some places atrophic.

The skin lesions differed from true scleroderma by virtue of a predominant involvement of the proximal parts of the extremities, especially in pelvic and shoulder girdles, whereas the facies and hands were least involved. There were no visceral lesions characteristic of scleroderma; X-ray of oesophagus and bones showed no abnormalities; concomitant hypogammaglobulinemia is also a rather unusual finding in true scleroderma.

Scleroderma-like lesions concomitant with dermatomyositis (sclerodermatomyositis) could be ruled out because the disease began in early infancy, ran a protracted, steadily progressive course. The transaminases, aldolase and phosphocreatine kinase—enzymes characteristic of muscle destruction—were normal, as also was electromyography.

In case 2, despite of strong similarity to case 1,

the scleroderma-like lesions were much more pronounced. However, even in this case the skin and muscle indurations were most evident in proximal parts of the extremities, and the hands were least involved. In the facies the skin was taut and hard, but with no atrophy of lips and nose. Internal organs, X-ray of bones and digestive tract were normal, and function tests (vascular and electrophysiological) showed no abnormalities characteristic of scleroderma.

As in case 1, sclerodermatomyositis could be excluded here too.

Glycogenosis was diagnosed on evidence of a biochemically established high level of glycogen in muscles. In no other muscle disease other than glycogenosis is the glycogen content considerably higher than normal, and in some muscular dystrophies, it may even be lower (12). The diagnosis of glycogenosis was confirmed by electronmicroscopic findings—unevenly distributed deposits of glycogen, larger in subsarcolemmal localization. The ischemic exercise also showed some abnormalities in the anaerobic glycogenolysis—a finding characteristic of glycogenoses.

In glycogen storage diseases there is a considerable accumulation of glycogen of normal or abnormal structure in the liver, muscles, heart, kidneys, and sometimes even erythrocytes.

Biochemical and enzymatic studies have shown the disease to result from a greatly reduced activity or absence of one of the enzymes responsible for the degradation of tissue glycogen (7, 11, 13, 30). The prevalent opinion now is that glycogenoses are, in general, autosomal hereditary diseases (7).

There are four clinical types of the disease: muscular, hepatic, hepato-muscular, and generalized. Determination of the enzymatic defect is decisive for the diagnosis.

According to the kind of enzymatic block described by Cori, six types of glycogenosis, and recently 8 types (Fig. 6), are already recognized (13). Tarui et al. (32), Thomson et al. (34), Satoyoshi & Kawa (26) as well as Layzer et al. (19) have demonstrated that in addition there are cases of muscular involvement due to other and previously unknown enzymatic defects, viz. involving deficiency of phosphofructokinase, phosphoglucomutase, or phosphohexoisomerase. Moreover, Gutman et al. (9) have described a case of glycogenosis in which no enzymatic defect could be detected in the pathway of glycogen degradation.

In our cases, although the patients' muscle glycogen level was elevated rather considerably in case 1, we also were unable to demonstrate, either directly or indirectly, any enzymatic defect in the pathway leading from glycogen to lactic acid. This means that our cases do not correspond to any known type of glycogen storage disease. Neither does the clinical picture correspond to any hitherto described glycogenosis.

It should be stressed that scleroderma-like lesions with concomitant mental retardation in case 1 were almost identical with our previous case of pseudoscleroderma in PKU (14) but all studies in this direction gave in the present case negative results.

It was possible, however, in both present patients to demonstrate deranged tryptophan metabolism in the indole acid pathway similar to that in PKU (6, 14). In PKU the deranged tryptophan metabolism results from its retarded intestinal absorption which may be related to the raised level of phenylalanine (6).

In our present cases without PKU, retarded intestinal absorption was not related to phenylalanine. It was indicated in case 1 by the curves after ingestion of phenylalanine (peak after 3 hours, normally after 1 to 1 $^{1}/_{2}$ hours), D-xylose (maximum concentration in the blood 2 $^{1}/_{2}$ hours after loading, normally after 1 $^{1}/_{2}$ at the most), and saccharose load (slowly decreasing curve after maximum level has been reached). The saccharose curve after the loading was similarly retarded in case 2, and a high level of total indoles as well as free and bound indole-acetic acids in urine was found in both patients which is also characteristic of retarded tryptophan absorption. The differences between the two cases consisted in the pronounced derangement of tryptophan metabolism in case 1 without loading whereas in case 2 it became evident after loading.

Skin and muscle indurations coexistent with retarded intestinal absorption of tryptophan are of special interest because some authors claim that the intestinal malabsorption syndrome also occurs in scleroderma (3, 15, 20).

The role of deranged tryptophan metabolism in the pathogenesis of scleroderma, as well as in the pathogenesis of pseudoscleroderma of different etiologies calls for further investigations.

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Received February 16, 1972

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