RESULTS

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Clinical features :

In Table (1), the final diagnosis of each patient is given together with the symptom[s] that first brought them to medical attention [presentation] and the clinical features which subsequently led to the suspicion of a metabolic disorder.

Metabolic myopathies presented with a great varity of clinical disorders. Deafness, ophthalmoplegia and encephalopathy were salient features in patient with mitochondrial myopathies. Ataxia, organomegaly and cardiomegaly were confined to those suffering from glycogen myopathies, Whereas short stature, mental retardation and seizures were present in the three metabolic groups.

The atypical group [Table 2] presneted with the same constellation of clinical signs and symptoms. We mention cases No. 18 and 19 in particular as both were presenting with demyelination of the white matter demostrable on megnetic resonance imaging in addition to a myopathic EMG and a moderate increase in CPK level.

The mean age as well as the mean duration of illness were significantly lower in patients with metabolic myopathies than in those with muscular dystrophy [Table 6].

Biochemical data :

Serum CPK activity :

Serum creatine phosphokinase activities in patients with established metabolic myopathies are shown in Table [3]. It is obvious

that even when muscle weakness is the only symptom, CPK may be normal or only mildly elevated.

Serum CPK was grossly abnormal in only 2 patients [case No. 5 and No. 15] with established metabolic myopathy and in 2 patients in the atypical group [case no. 8 and 9]. In dystrophic patient, CPK was highly elevated with statistically significant difference [Table 6].

Blood Lactate :

Fasting blood lactate concentration are shown in Tables [3 & 4] from which it can be seen that most patients had a normal fasting blood lactate, only case No. 5 with mitochondiral myopathy had an increased value.

2 cases [No. 25 and No. 29] with Duchenne muscular dystrophy {DMD} had a high blood lactate thus demonstrating that blood lactate is not a sensitive marker in diagnosis of metabolic myopathies.

Serum L-Carntine :

The majority of patients with established or suspected metabolic myopathies suffered from Hypocarnitinaemia [Table 3] and serum L-carnitine was significantly lower in the metabolic group when compared to the dystrophic one [Table 6]. No significant difference was observed between the different subgroups of metabolic myopathies as well as between the established cases and the atypical group, therefore serum L-carnitine could be a useful biochemical marker in suspecting a methabolic disorder.

Muscle histopathology and electron microscopic study :

In this study, skeletal muscle biopsy specimens were obtained from 34 patients; 24 with suspected metabolic myopathies and 10 with muscular dystrophies.

Muscle biopsy was helpful in confirming the diagnosis in 16/24 patients with suspected metabolic myopathies.

In 5/16 patients, muscle biopsies showed subsarcolemmal aggregates of abnormally larger and bizarre shaped mitochondria consistent with mitochondrial myopathy [Figs. 1 & 2].

In 7/16 patients, variable sized vacuoles within the myofibrils representing lakes of glycogen in the subsarcolemmal zone were demonstrable in their muscle biopsies [Fig. 3 & 4]. The biopsy of one of these patients with glycogen storage myopathy showed bizarre mitochondira with abnormally large shaped cristae in addition to the subsarcolemmal glycogen vacuoles suggesting the diagnosis of glycogen mitochondrial myopathy.

Muscle biopsies in 4/16 patients revealed the presence of lipid vacuoles inside the muscle fibres consistent with the diagnosis of lipid myopathy [Fig. 5 & 6].

In the remaining 8 patients in whom the clinical pictures was highly suggestive of a metabolic myopathy, both light and electron microscopic study of their muscle biopsy specimen failed to demonstrate a definite metabolic abnormality.

Histological study of muscle biopsy specimens obtained from the 10 control patients was consistent with a dystrophic pattern which showed a variation in fibre size, with atrophic, hypertrophic, necrotic and regenerative fibres with prominent fatty infltration between bundles of skeletal muscle fibres.

Immunohistochemistry using sys II monoclonal antibodies directed against the carboxyl terminus of the dystrophin molecule was performed in 4 patients using the immunoperoxidase technique. Cases No. 25, 28 & 29 showed an almost total absence of immunostaining around individual muscle fibres, a picture consistent with Duchenne muscular dystrophy [Fig. 7].

Table (1): Clinical Summary of Patients with Established Metabolic Myopathies (16 cases).

Case No.	Age (years)	Sex	Duration (years)	Presentation	Factor leading to diagnosis	Hisstopathological Diagnosis
1	13	M	3	Proximal myopathy	Deafness+short Stature	Mitochonrial Myopathy (SSAM)
2	3	F	2.5	Development delay+ sezure+hypotonia	Encephalopathy+Ataxia + Ophthalmoplegia	Mitochondrial Myopathy (SSAM)
3	2	F	1.5	Delayed waking	Hypotonia, mypathic EMG, mild CPK ↑↑ affected sister.	Mitochondrial myopathy (SSAM)
4	10	M	1.5	Proximal myopathy	Normal CPK+ myopathic EMG.	Mitochondrial myopthy (SSAM)
5	12	M	3	Proximal myopathy	Ophthalmoplegia	Mitochonrial myopthy (SSAM)
6	5	M	1.5	Muscular cramps on exertion +proximal myopathy	Moderate CPK ↑↑ Myopathic EMG, short stature	Glycogen myopathy
7	14	F	3	Ataxia + proximal myopathy	Cardiac affection + mild CPK ↑↑ + myopathic EMG	Glycogen myopathy
8	18	F	10	Generalised weakness & wasting (WCB) + ataxia	Normal CPK + Endocrinopathy (DM)	Glycogen myopathy
9	8	M	1	muscular cramps on exertion	Mild CPK ↑↑ +short stature, mild muscle wasting	Glcogen myopathy
10	5	M	1.5	Proximal myopathy Muscle cramps	MR+ seizures+ normal CPK + affected sister	Glycogen myopathy
11	1	F	0.5	Floppy infant	Generalised hypot. Myopathic EMG + normal CPK	Glycogen myopathy
12	3	F	2	Floppy infant	Hepatomegaly + cardiomypathy + mild CPK ↑↑	Glycogen myopathy
13	13	M	10	Generalized weakness & wasting (WCB)	Mild CPK ↑↑ + affected sister	Lipid myopathy
14	8	F	4	Proximal myopathy+ tiptoe walking	Mild CPK ↑↑ affected brother	Lipid myopathy
15	8	M	4	Proximal myopathy	Seizures + MR	Lipid myopathy
16	5	M	4	Proximal myopathy	Myopathic EMG + normal CPK	Lipid myopathy

DM: Diabetes mellitus.
MR: Mental retardation.
SSAM: Subsarcolemmal aggregation of mitochondria.
WCB: Wheel chair bound.
Cases No. 7, 8 & 9 belong to the same family (2sisters and 1 brother).
Cases No. 13 & 14 belong to the same family.

Table (2) : Clinical Summary of Patients with Suspected Metabolic Myopathies (8 cases).

Case No.	Age (years)	Sex	Duration (years)	Presentation	Factors leading to suspected diagnosis	Histopathological Diagnosis
17	1.5	M	1.5	Floppy infant	Bilateral ptosis + seizures + nystagmus + neurogenic EMG	Active myopathy
18	8	M	1.5	Encephalopathy	Myopathic EMG + moderate ↑↑ in CPK+ high signal lesions (T2 weighted MRI)	Non- specific Myopathic changes
19	8	F	1	Ataxia Encephalopathy	Myopathic EMG + Pseudoypertrophy of calves +high signal lesions (T2 weighted MRI)	Non-specific Myopathic changes
20	3	M	2.5	Floppy infant	*MR + Serizures	Normal Biopsy
21	4	M	3	Floppy infant	Profound hypotonia + mental retardation+ seizures	Normal Biopsy
22	4	F	3	Proximal myopathy	Normal CPK - spordic	Non-specific myopathy
23	2	M	2	Floppy infant	MR+Ophthalmopegia	Normal Biopsy
24	1.5	F	1	Floppy infant	MR+seizures+normal CPK	Neurogenic atrophy

MR: Mental retardation.

Table (3) : Biochemical data of patients with both established and suspected metabolilc myopathies (No.=24).

Case No.	Biochemistry			Histopathology
	CPK μ / L	Lactate Mmol/L	L-carnitine μmol/L	
1	128	1.1	33.3	Mitochondrial Myopathy
2	40	1.2	31.8	Mitochondrial Myopathy
3	256	1.5	30.4	Mitochondrial Myopathy
4	70	1.6	10.5	Mitochondrial Myopathy
5	3500	2.8*	30.7	Mitochondrial Myopathy
6	405	1.1	27.7	Glycogen Myopathy
7	230	1.2	18.6	Glycogen Myopathy
8	56	0.9	42.3	Glycogen Myopathy
9	238	1.2	20.8	Glycogen Myopathy
10	17	1.2	18.8	Glycogen Myopathy
11	8	1.1	21.6	Glycogen Myopathy
12	249	0.9	42.3	Glycogen Myopathy
13	200	1.2	36.2	Lipid Myopathy
14	215	1.3	33.3	Lipid Myopathy
15	14000	1.2	69	Lipid Myopathy
16	144	1.6	21	Lipid Myopathy
17	100	1.3	18.8	Active Myopathy
18	840	1.7	31.8	Non-Specific Myopathy
19	490	1.1	21.6	Non-Specific Myopathy
20	15	1.2	19.8	Normal Muscle Biopsy
21	31	1.2	26.6	Normal Muscle Biopsy
22	45	1.3	16.9	Myopathic Picture
23	20	1.7	32.4	Normal Biopsy
24	50	1.2	33.8	Neurogenic Atrophy

Table (4) : Clinical and Biochemical Parameters in Muscular Dystrophy patients (10).

No. of Cases	Age (years)	Sex	Duration of illness (years)	Biochemistry			Comments
				CPK µ/L	Lactate mmol/L	L-carnitine µmol/L	
25	11	M	6	1467	4.1	43.6	Sporadic case,-ve family history. Immunohistochemistry showed absence of immunoreactive fibres.
26	14	F	3	2153	1.3	39.2	+ve family history with a younger sister affected (WCB). Immunohistochemistry showed a mosaic pattern consistent with MC-DMD.
27	6	F	4	588	1.2	41.6	One affected brother, a myopathic EMG, a dystropic picture on muscle biopsy.
28	10Y	M	5	231	0.9	41.8	Immunohistochemistry showed variable staining intesity copmatible with Becker dystrophin phenotype, sporadic case.
29	15	M	10	1143	2.8	44.4	Sporaadic-wheel chair bound, myopathic EMG & dystrophic picture on muscle biopsy.
30	8	M	3	8600	o.7	37	Duchenne dystrophin phenotype on immunohistochemistry, Sporadic case.
31	12	M	7	23200	0.4	51.2	Dystrophic picture on muscle biopsy-sporadic
32	8	M	3	140	1.1	35.2	Dystropic picture on muscle biopsy- sporadic-wheel chair bound.
33	49	M	9	506	1.1	35.3	Weakness, hypotonia and hyporeflexia since birth-EM: contsistent with advanced stage of muscle dystrophy-compatible with congenital muscular dystrophy- sporadic case.
34	10	M	6	13240	0.9	49.5	Dystrophic picture on muscle biopsy-sporadic case.

EM:Electron microscopy.
FM: Family history.
MC-DMD:Manifesting carrier of Duchenne muscular dystrophy.
WCB: Wheel chair bound.

Table (5) : Salient Clinical Features in Metabolic Myopathy Patients as Compared to muscular Dystrophy Patients.

Clinical features	Metabolic Cases (24)		Dystrophic cases (10)	
	No.	%	No.	%
***General exam:**				
-Family History	2	8.3	2	20
-Consanguinity	16	66.6	3	33
-Short Stature	3	12.5	2	20
-Endocrinopathy	1	4.2	0	0
-Organomegaly	1	4.2	0	0
-Cardiac Affection	2	8.3	0	0
***Neurological:**				
-Encephalopathy	3	12.5	-	-
-Mental Retardation	15	62.5	2	20
-Seizures	7	29.5	-	-
-Ataxia	4	16.4	-	-
-Ophthalmoplegia	4	16.4	-	-
-Hearing defect	1	4.2	-	-
-Motor examination				
-Weakness:				
-Proximal	12	50	8	80
-Generalised	12	50	2	20
-Hypotonia	21	83.3	10	100
-Hyporeflexia	18	73.8	10	100
Pseudohypertropy	6	24.6	7	70
EMG:				
-Normal	8	32.8	-	-
-Myopathic	15	62.5	10	100
-Neuropathic	1	4.1	-	-
CPK:				
-Mean ± SD	891± 2891		3038± 4359	

Table (6) : Comparative Study of Biochemical Parameters in the Studied Groups.

Studied Groups	Studied Variables				
	Age (yrs) Mean ± SD	**Duration Mean ± SD**	**CPK (U/ L) Mean ± SD**	**Lactate mmol/L Mean ± SD**	**L-carnitine mmol/L Mean ± SD**
Metabolic (24)/ Dystrophic (10) P value	6.70± 4.7 10.10 ± 2.8 <0.01*	2.79± 2.45 4.9 ± 3 <0.01*	891±2897 3038 ± 4359 <0.01*	1.32 ± 0.38 1.45± 1.12 > 0.05	28.50 ± 11.6 43.2 ± 5.30 <0.01*
Mitochondrial (5)/ Lipid (4) P value	8 ± 5.14 8.3 ± 3.31 >0.05	2.30 ± 0.75 5.50 ± 3 <0.01*	798 ± 1512 3639 ± 6909 > 0.05	1.64 ± 0.68 1.32 ± 0.18 > 0.05	27.34 ± 9.48 40.02 ± 20.47 >0.05
Mitochondrial (5)/ Glycogen (7) P value	8 ± 5.14 7.85 ± 6.44 >0.05	2.30 ± 0.75 2.70 ± 3.31 > 0.05	798 ±1512 179 ± 153 >0.05	1.64 ± 0.68 1.08 ± 0.13 <0.05*	27.34 ± 9.48 26.50 ± 9.3 >0.05
Glycogen (7)/ Lipid (4) P value	7.85 ± 6.44 8.50 ± 3.31 >0.05	2.70 ± 3.31 5.50 ± 3 <0.05	179 ± 153 3639.7± 6909 >0.05	1.08 ± 0.13 1.32 ± 0.18 >0.05	26.57 ± 9.33 40.02 ± 20.47 >0.05
**Histologically confirmed group(16)/ atypical group (8) P value	8.06 ± 5.09 4.18 ± 2.50 >0.05	3.28 ± 2.85 1.81 ± 0.84 >0.05	1237.8 ± 350.5 198 ± 303 >0.05	21.31 ± 350.5 1.33 ± 0.23 > 0.05	30.17 ± 13.31 25.21 ± 6.79 >0.05
Dystrophic group (10)/ Atypical group (8) P value	10.1 ± 2.8 4.18 ± 2.5 <0.001*	4.9 ± 2.2 1.81 ± 0.84 <0.001*	3038 ± 4359 198 ± 303 <0.001*	1.45 ± 1.12 1.33 ± 0.23 >0.05	43.2 ± 5.30 25.21 ± 6.79 <0.001*
Dystrophic group (10)/ Metabolic group (16) P value	10.1 ± 2.8 8.05 ± 0.84 >0.05	4.9 ± 2.2 3.23 ± 2.85 <0.05*	3038 ± 4359 1237 ± 3505.2 <0.01*	1.45 ± 1.12 1.31 ± 0.46 >0.05	43.20 ± 5.30 13.31 ± 3.11 <0.01*

*Statistically significant difference.

** No statistically signficant difference was observed between the histologically confirmed and the atypical group in the variable studied parameters.

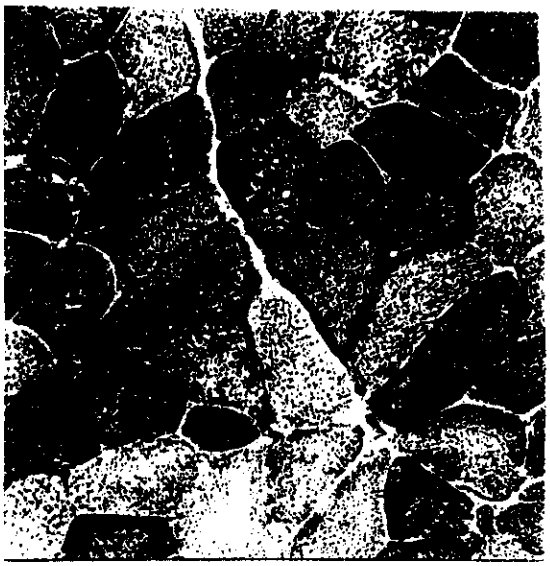


Fig.(1): Muscle biopsy obtained from case No. (5) demonstrating a dense suubsarcolemmal accumlations of enzyme (NADH TR, x175).

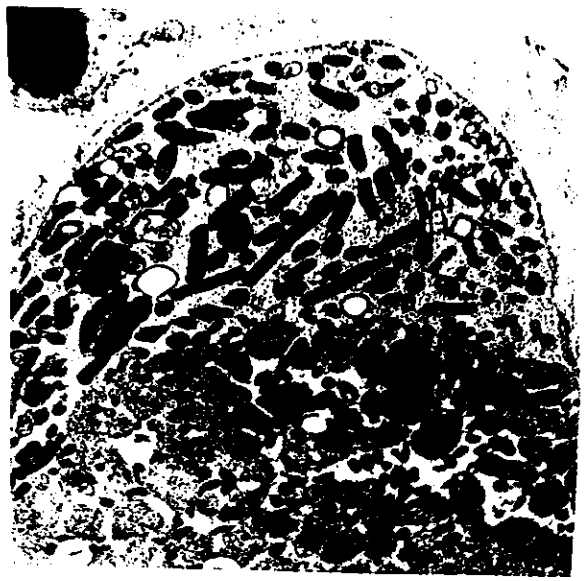


Fig.(2): Increased number of mitochondria found as large subsarcolemmal aggregates. (Electron microscopy, x 9600).

Fig.(3):Excess glycogen storage demonstrated by increased PAS uptake (PAS, x200).

Fig. (4): Abnormal amount of stored glycogen are seen occupying a large proportion of the fibres (Electron microscopy, x10000).

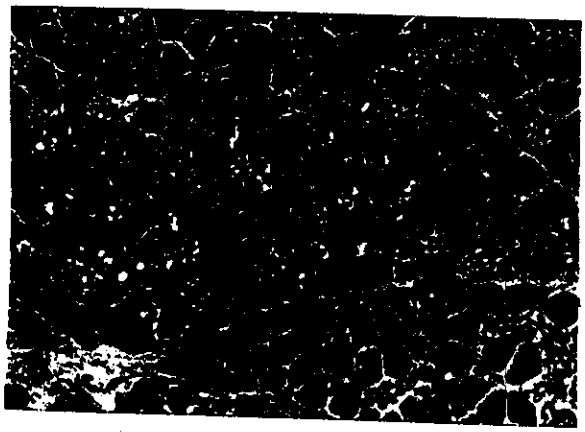


Fig. (5): Muscle biopsy obtained from case No. (13). Most fibres are vacuolated to some degree (H&E, x280).

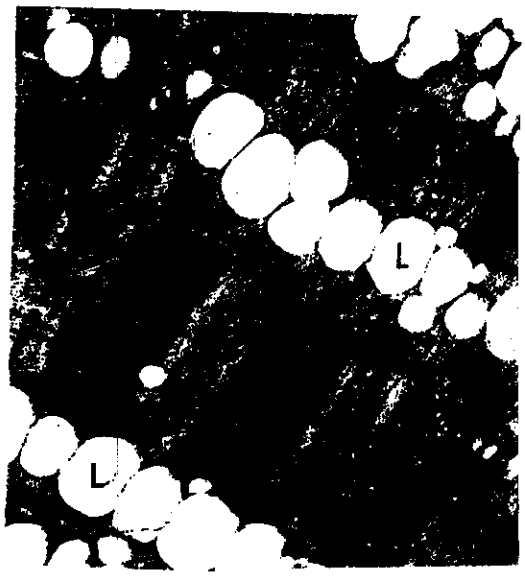


Fig .(6): Excess lipids are seen as droplets between myofibrils. (Electron microscopy, x 13750).

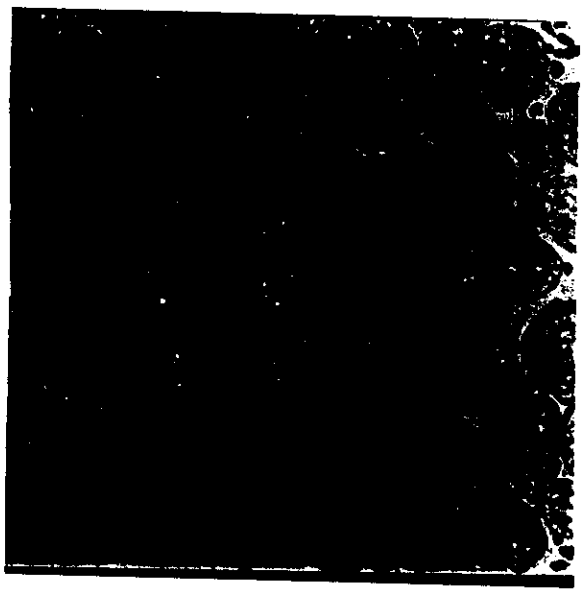


Fig. (7) : Immunohistochemistry showing complete absence of immunoreactive fibres: a Duchenne dystropin phenotype (immuno-peroxidase, x 200).

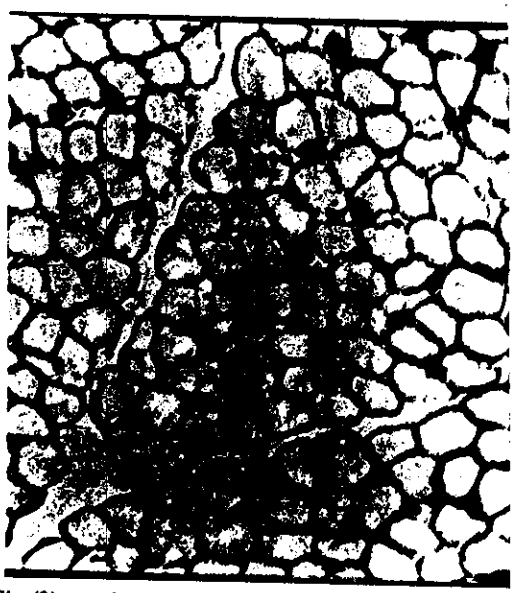
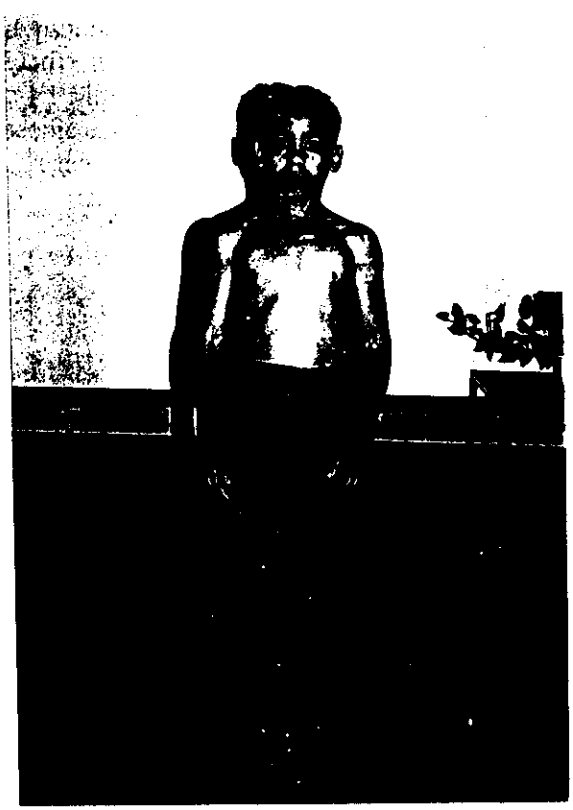


Fig.(8): Immunohistochimistry of normal muscle biopsy demonstrating the appearance of dystrophin as a continous brown ring along prephary of each muscle fiber .

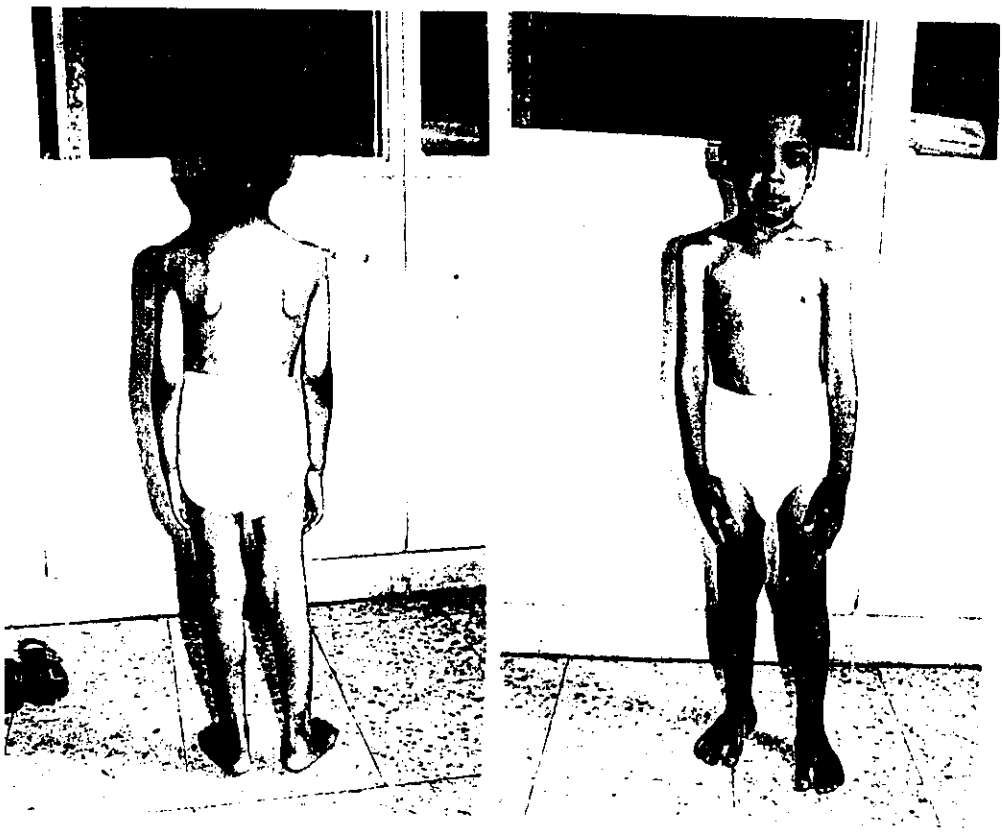


- *Case No. (1) :* This 13-year- old child presented with history of frequent falls, difficult in climbing stairs and defective hearing of 3-year- duration. Clinical examination showed marked short stature, proximal muscle weakness, hypotonia, hyporeflexia and psudohypertrophy of calf muscle. Audiometry revealed a bilateral conductive hearing defect. Investigations revealed : CPK 128 U/L, serum lactate 1.1 Mmol/L and serum L. carnitine 33.3 umol/L. Light and electron microscopic examination of muscle biopsy specimen showed subsarcolemmal aggregates of abnormal size and shape mitochondria..

- *Case No. (2) :* This 3-year- old girl presented with global developmental delay and generalized tonic - clonic seizures started at the age of six months. Neurological examination revealed generalized hypotonia, normal reflexes, mental subnormality, excess irritability, unsteadiness of gait and left convergent squint.

  Investigations revealed : CPK 40 U/L, serum lactate 1.2 M mol/L, serum L. carnitine 31.8 u mol/L, Brain C.T. Normal, TORCH screen Normal, EMG Normal. Light and electron microscopic examination of muscle biopsy specimen revealed subsarcolemmal aggregates of increased number of mitochondira, mitochondria of abnormal shape were also seen between the myofibrilis.

- *Case No. (3) :* This 2-year-old girl presented with motor developmental delay (as no walking was achieved at the time of clinical examination). Neurological examination showed marked hypotonia, hyporeflexia, mild mental subnormality and a fair complexion. CPK 256 U/L, serum lactate 1.5 Mmol/L, serum L. Carnitine 30.4 umol/L. EMG myopathic. Light and electron microscopic examination revealed subsarcolemmal aggregates of abnormal size and shape mitochondria.



- *Case No. (6) :* This 5-year- old child had a history of muscular cramps on exercise, difficulty in climbing stairs and frequent falls of 1.5 year-duration. Clinical examination showed short stature, mild muscle wasting, normal tone and mild hyporeflexia. Investigations revealed CPK 405U/L, serum lactate. 1.1 Mmol/L, serum L. carnitine 27.7 umol/L. EMG myopathic. Light and electronic microscopic examination showed lackes of glycogen situated in the subsarcolemmal zone as well as in between myofibrilis. Mitochondria are large with abnormal cristae, many contain glycogen.