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Familial Spinal Muscular Atrophy with Additional Features : A family report

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รายงานผู้ป่วยครอบครัวผู้ป่วย 1 ครอบครัว : โรค spinal muscular atrophy ที่มีลักษณะเพิ่มเติมทางคลินิก

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บทคัดย่อ

โดยทั่วไป spinal muscular atrophy (SMA) เป็นโรคที่มีอาการแสดงหลายอย่าง แต่ผู้ป่วยที่เป็นโรค SMA ร่วมกับการมีอาการแสดงเพิ่มเติมทางคลินิก เช่น ataxia, retinitis pigmentosa ฯลฯ นั้น พบได้น้อยมาก อย่างไรก็ตาม มีรายงานในหลายประเทศที่มีผู้ป่วยโรคนี้ที่มีลักษณะดังกล่าวแต่จากการค้นคว้างานวิจัยที่ผ่านมา พบว่า ประเทศไทยยังไม่เคยพบผู้ป่วยที่มีอาการดังกล่าวเลย รายงานครั้งนี้เป็นการกล่าวถึงครอบครัวคนไทย 1 ครอบครัว ประกอบด้วยสมาชิก 4 คน ที่เป็นโรคดังกล่าว ซึ่งอาการแสดงพิเศษที่พบนั้นมีดังนี้ ataxia, retinitis pigmentosa และ optic atrophy

Abstract

There is considerable variation in the types of spinal muscular atrophies. SMA with additional features are unusual. There have been reports in many countries with specific cases describing patients with these variations. Literary reviews literature in Thailand have never reported such cases. This report is about a single Thai family of members. Four members have been affected with SMA with additional features of ataxic, retinitis pigmentosa and optic atrophy.

Spinal muscular atrophies (SMA) involve primarily the motor neurons of the spinal cord, often the bulbar motor neuclei, but rarely the pyramidal tract.[7] SMA is one of the most devasting genetically determined neurological disorder in childhood. In general, the earlier the presentation of weakness, the more rapid the course and the poorer the prognosis. Their clinical manifestations are proximal muscle weakness, muscle atrophy of extremities, fasciculations and early loss of tendon reflexes. The sensory system is intact. The other forms of spinal muscular atrophy are extremely variable in their age of onset, severity and rate of progression.[7,8] Electromyography is the most reliable diagnostic criteria.[6] The creatine kinase level in spinal muscular atrophy is normal in over 70 percent of cases. Increases are generally small, rarely up to 1000 I.U./litre. Cerebrospinal fluid chemistry is normal. Tendon reflexes are almost normal, and in about 2% some tendon reflexes are hyperactive, but in such patients other reflexes are diminished or absent.[9] These disorders are genetically autosomal recessive, autosomal dominant, sex-linked recessive or sex-linked dominant.[1,2,3,5,6,9] They vary in age of onset, severity, rate of progression and clinical manifestation.[7] The course of the disease may be improved (2%), static (13%) or deteriorate (85%).[6] Spinal muscular atrophy with additional features have been reported in some countries.[9,6,4] These clinical features include external ophthalmoplegia, facial weakness, scoliosis, dysarthria, mental retardation, ataxia and visual failure.[9] In Thailand, such cases have never been reported. This report is about a single Thai family of 4 members, three with such features (figure 1). Details follows.

Case I

Case I, the first son, is a 23 year old man. He was first noted to be weak at 15 years old. He fell frequently and had difficulty in arising. It was later noted that he had some difficulty in using his hand. Gestation, delivery and development were normal. He has had no serious illness and is considered to be of normal intelligence. He had progressive ataxic gait and dysarthria. Presently he can not walk but he can arise from the supine or sitting position. He ambulates by wheel chair. On examination he had retinitis pigmentosa and optic atrophy. There was asymmetrical weakness of the extremities. Lower extremities were weaker than upper extremities. In the lower extremities the weakness was more pronounced proximally. Atrophy of intrinsic hand and leg muscles were found. The patellar and Achilles tendon jerk were hypoactive. There were cerebellar signs and fasciculation potentials. The sensory system was normal.

Laboratory Studies

The result from the electrocardiogram, x-ray of the chest and blood studies (Hb, Wbc, ESR, VDRL, urea nitrogen, fasting glucose, SGOT, SGPT, serum electrolyte) were normal. The creatine kinase level was grossly elevated (1458 U/L). Motor nerve conduction velocity (MNCV) was normal (Table I) whereas sensory nerve conduction velocity (SNCV) was slow in bilateral median and ulnar nerves. No sensory action potential was elicited on stimulating both sural nerves. (Table II) The

electromyogram obtained from the extensor carpi radialis (ECR) and first dorsal interossious of the right arm showed increased insertional activity and incomplete interference pattern. Fibrillation and positive sharp wave potentials were present. Giant motor unit action potentials were seen (11-22.6 mv). The duration of the motor unit potentials was 9.8-12.5 msec. (Table III)

Case II

Case II, the second son, is a 22 year old man. He was first noted to be weak at 15 years old. He had even been a boxer. It was later noted that he had some difficulty in using his limbs. He had no fever or convulsion previously. He had dysarthria, difficulty in walking and poor visual system. Gestation and delivery were normal. He had normal development. He has had no serious illness and is considered to be of normal intelligence. He had to be taken away from school due to his poor visual system. He can arise from the supine or sitting position. He walks with ataxic gait. He had tremulous voice. On examination, he had retinitis pigmentosa and optic atrophy. (figure 2). His problem is more from ataxia than weakness. There was no significant weakness of extremities. The muscle tone was decreased. The patellar and Achilles tendon jerk were hypoactive. Cerebellar sign and fasciculation potentials were found. The sensory system was normal.

Laboratory Studies

The results from the electrocardiogram, x-ray of chest and blood studies (Hb, wbc, ESR, VDRL, urea nitrogen, fasting glucose, SGOT, SGPT, serum electrolyte) were normal. The creatine kinase level was increased (588 U/L). Slow MNCV was measured in bilateral median, ulnar, common peroneal and posterior tibial nerves. (Table I) Slow SNCV was measured in bilateral median and ulnar nerves. No sensory action potential was elicited on stimulating both sural nerves. (Table II) The electromyogram obtained from deltoid and ECR of the left arm showed increased insertional activities and incomplete interference pattern. Fibrillation, positive sharp wave and fasciculation potentials were present. Giant motor unit action potentials were seen (20-30 mv). The duration of motor unit potentials was 6.0-9.5 msec. (Table III) Biopsy of the left sural nerve revealed normal.

Case III

Case III, the third son, is a 21 year old man. He was first noted to be ataxic and weak at 17 years old. He had difficulty in seeing and walking. It was later noted that he had some difficulty in speaking and using his hands. He had to be taken away from school due to poor vision. He has never had convulsion associated with fever. Gestation, delivery and development were normal. He has had no serious illness and is considered to be of normal intelligence. He could arise from the supine or sitting positions but with ataxia. He walked with ataxic gait. He had dysarthria. On examination there were bilateral internal squints. He had optic atrophy and retinitis pigmentosa. His problem was more from ataxia than weakness. The muscle power was nearly normal. The muscle tone was decreased. The pattellar and Achilles tendon jerk were hypoactive. Cerebellar sign and fasciculation potentials were found. The sensory system was normal.

Laboratories Studies

The result from the electrocardiogram, x-ray of the chest and blood studies (Hb, Wbc, ESR, VDRL, urea nitrogen, fasting glucose, SGOT, SGPT, serum electrolyte) were normal. The creatine kinase level was increased (272 U/L). Normal MNCV was measured in bilateral ulnar nerves, but slow MNCV was measured in bilateral median,

common peroneal and posterior tibial nerves. (Table I) Normal SNCV was measured in bilateral median, ulnar and sural nerves. (Table II) The electromyogram obtained from first dorsal interosseous and deltoid of the right arm showed increased insertional activities and incomplete interference pattern. Fibrillation, positive sharp wave and fasciculation potentials were present. Giant motor unit action potentials were seen (25-29 mv). (Table III) The duration of motor unit potentials was 5.9-10.2 msec. CT scan showed cerebellar atrophy. (figure 3)

Case IV

The father, is a 46-year old man, presently employed as a laborer. Weak since childhood, he began to walk at 7 years old and has continued up to the present day. Slowly progressive proximal limb weakness developed especially in the upper extremities without visual disturbance. He walked with a waddling gait. Examination of the cranial nerves were normal. Postiive findings on examination were limited to the neuromuscular system. Wasting was evident in the muscle of the right shoulder, arm, left scapular area and calf muscles (figure 4). There was no significant weakness of the lower extremities. The muscle tone was decreased. No fasciculation potentials was seen. The tendon jerks were hyporeflexia. Examination of the sensory system and cerebellar sign revealed no deficit.

Laboratory Studies

The results from the electrocardiogram, x-ray of the chest and blood studies (Hb, Wbc, ESR, VDRL, urea nitrogen, fasting glucose, SGOT, SGPT, serum electrolyte) were normal. The creatine kinase level was slightly increased (170 U/L). Normal MNCV were measured in bilateral median and ulnar nerves. (Table I) Normal SNCV were measured in bilateral sural nerves. (Table II) The electromyogram obtained from the biceps and ECR of the right arm showed decreased insertional activity, no denervation pattern and incomplete interference patern. Giant motor unit action potentials were seen (11-28 mv). The duration of the motor unit potentials was 10.0-15.0 msec. (Table III)

Discussion

The father (case IV) is the least severely affected living member. He is still walking independently but there is marked atrophy of the proximal muscles. The tendon jerks are absent throughout. The remainder of the neurological examination reveals no significant abnormality. The three sons (Case I-II-III) were admitted to the ward at the same time. All felt that weakness and ataxia were evident in adolescence. It was first noted as difficulty in ambulation due to ataxia. The weakness was slowly progressive and all had noted the more recent development of proximal weakness. The first son reported above, was the most severely involved. His problem was both weakness and ataxia. The third son was the most ataxic, but he is still walking independently. The second son was the least involved. He is still walking independently with good stability. He can do all activities of daily living totally independently. With regard to hand functions, he can reach out, grasp, carry and voluntarily release. He can do fine movement well. With regard to vocational counseling, the rehabilitation team advised a weaver's job at home. All cases except case I have visual dysfunction which were evidenced by retinitis pigmentosa and optic atrophy. The interesting features of this Thai family are that father only has proximal spinal muscular atrophy and the onset of disease was early as 3 year old whereas all his sons have distinctive features that included later onset of spinal muscular atrophy (15 year old), cerebellar ataxia, optic atrophy, retinitis pigmentosa and had more disability.

This variation of phenotypic features was described by a few authors. Pearn et al in 1978, briefly described two brothers with pigmentary retinopathy, cerebellar atrophy[3]. Furakawa et al in 1968, described a number of a Japanese family in whom onset of a gait disturbance and visual failure occurred in late childhood. The signs consisted of distal muscular atrophy, ataxia, and retinitis pigmentosa[10]. This family inherited as autosomal dominant. To our knowledge, this family probably is the largest family reported to have this associations. The associations between spinal muscular atrophy, cerebellar ataxia, retinitis pigmentosa may share some basic mechanism at the gene level, which awaits for elucidation in the future. Members of this Thai family have exhibited in more than one generation the presence of a slowly progressive muscular weakness associated with atrophy, proximal muscles weakness, hyporeflexia, ataxia and poor vision. Ataxia was noted peceding all other findings. The living affected adults have marked disabilities, but all have been able to lead relatively normal lives. Because of insidious onset and slow progression, it is not possible to decide whether the disease is appearing at an earlier age or whether it is being detected late because of the patient's unawareness. There have been a number of case reports describing patients and the various modes of inheritance.[1,2,3,5,6,9] The inheritance of this family appears to be sex linked recessive or autosomal dominant as evidenced by the pedigree (figure 5). The involved members of this family are clinically different from those patients described by other reports.[1,2,3,4,5,6,9] Although the nerve biopsy in case III of the left sural nerve was normal, the electromyography was compatible with a neurogenic lesion. There was no myopathic process in electromyography. The long survival is not compatible with the usual course of some types in SMA.

Conclusion

Three cases of SMA were described which showed additional features of ataxic, retinitis pigmentosa and optic atrophy. This represents the first report of such cases in Thailand.

Reference

1. Armstrong RM, Fogelson MH, Silberberg DH. Familial proximal spinal muscular atrophy. Arch Neurol 1966; 14: 208-12.
2. Hausmanowa-Petrusewicz I, Zaremba J, Borkowska J, Prot J. Genetic investigations on chronic forms of infantile and Juvenile spinal muscular atrophy. J Neurol 1976;213:335-46.
3. Pearn J. Autosomal dominant spinal muscular atrophy.J Neurol. Sci 1978; 38:236-75.
4. Bundey S, Lovelace RE.A clinical and genetic study of chronic proximal spinal muscular atrophy. Brain 1975; 98:455-72.
5. Pearn JH, Gardner-Medwin D. Wilson J. A clinical study of chronic childhood spinal muscular atrophy. J Neurol Sci 1978;38:23-37.
6. Emery AEH, Hausmanowa-Petrusewicz I, Davie AM, Holloway S, Skinner R, Borkowska J. International collaborative study of the spinal muscular atrophies.J Neurol Sci 1976;29:83-94.
7. Wiechers DO. Motor unit potentials in disease. In : Johnson EW, ed. Practical Electromyography. 2nd ed. London : William & Wilkins, 1988: 55-6.
8. Kimura J. Electrodiagnosis in diseases of nerve and muscle : principle and practice. Philadelphia : F.A. Davis 1983: 431-40.
9. Bundey S. Genetics and Neurology. Edinburgh: Churchill Livingstone, 1985: 172-90.
10. Furakawa T, Takasi A, Nakao K, Sugita H, Tsukagoshi H, Tsubaki T. Hereditary muscular atrophy with ataxia, retinitis pigmentosa and diabetis mellitus. Neurology 1968;18:942-7.

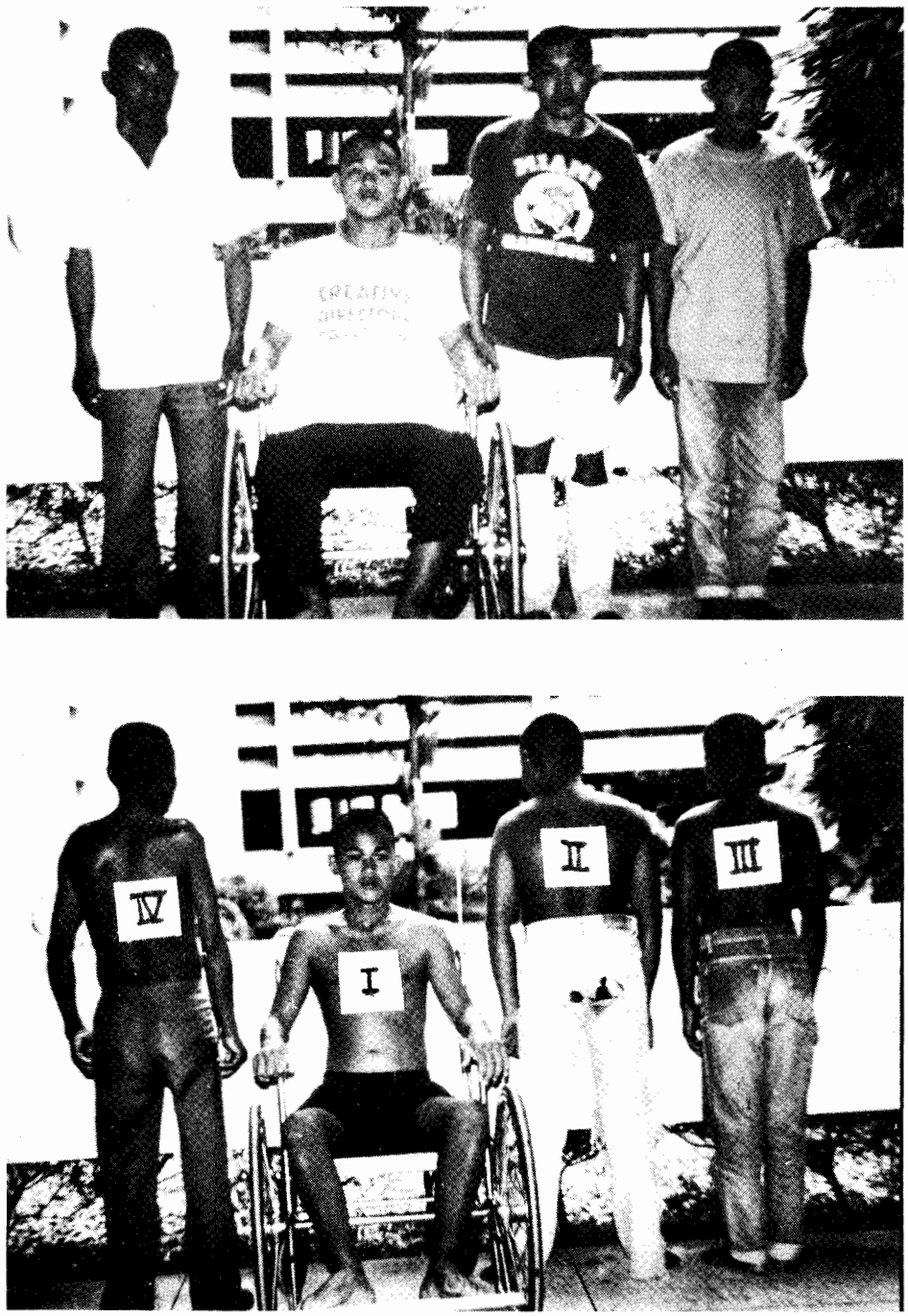


Figure I showed Thai family of 4 members

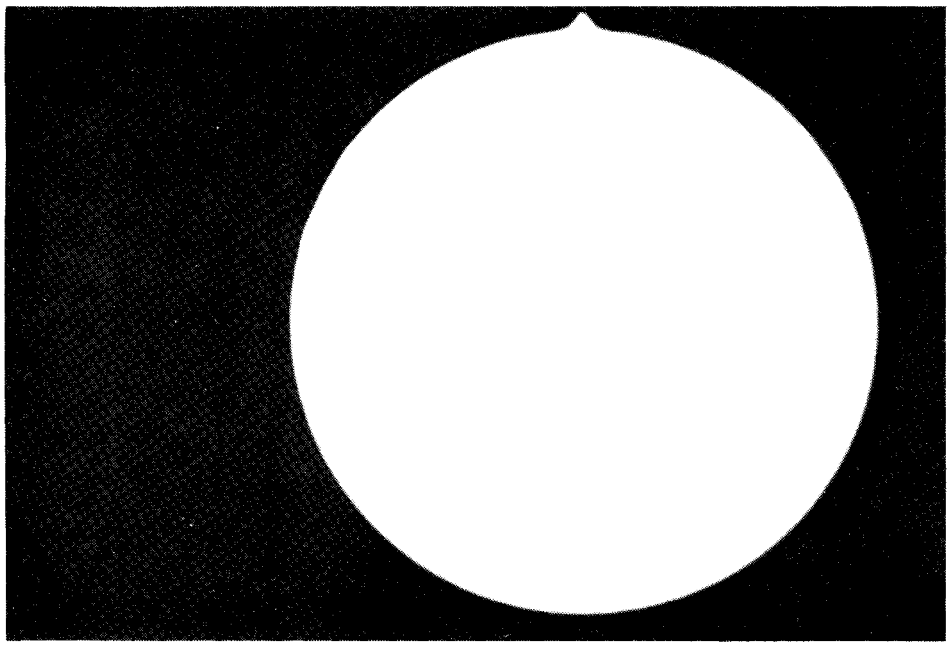


Figure II showed retinitis pigmentosa and optic atrophy of case II

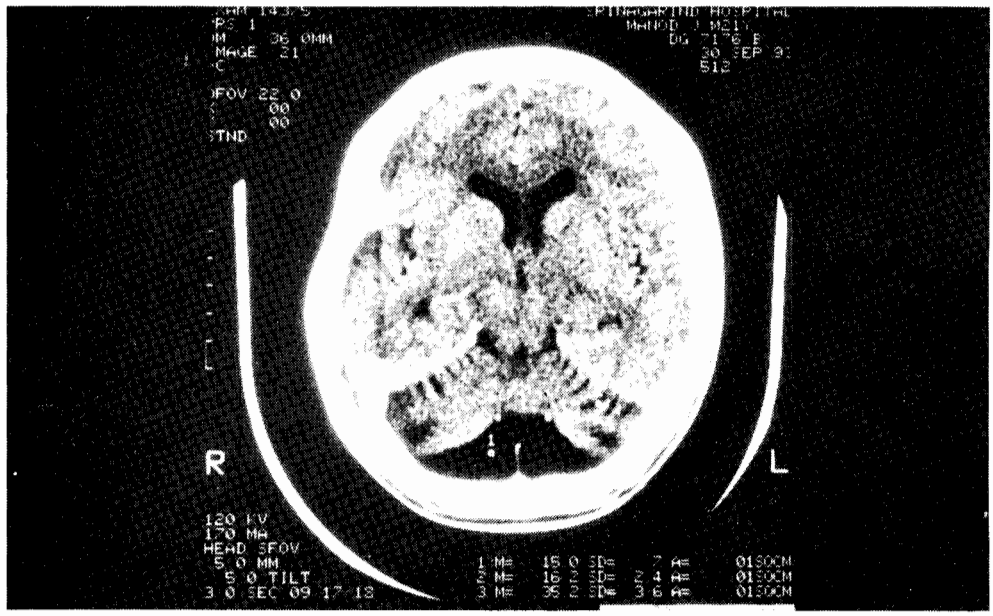


Figure III showed cerebrellar atrophy from CT scan

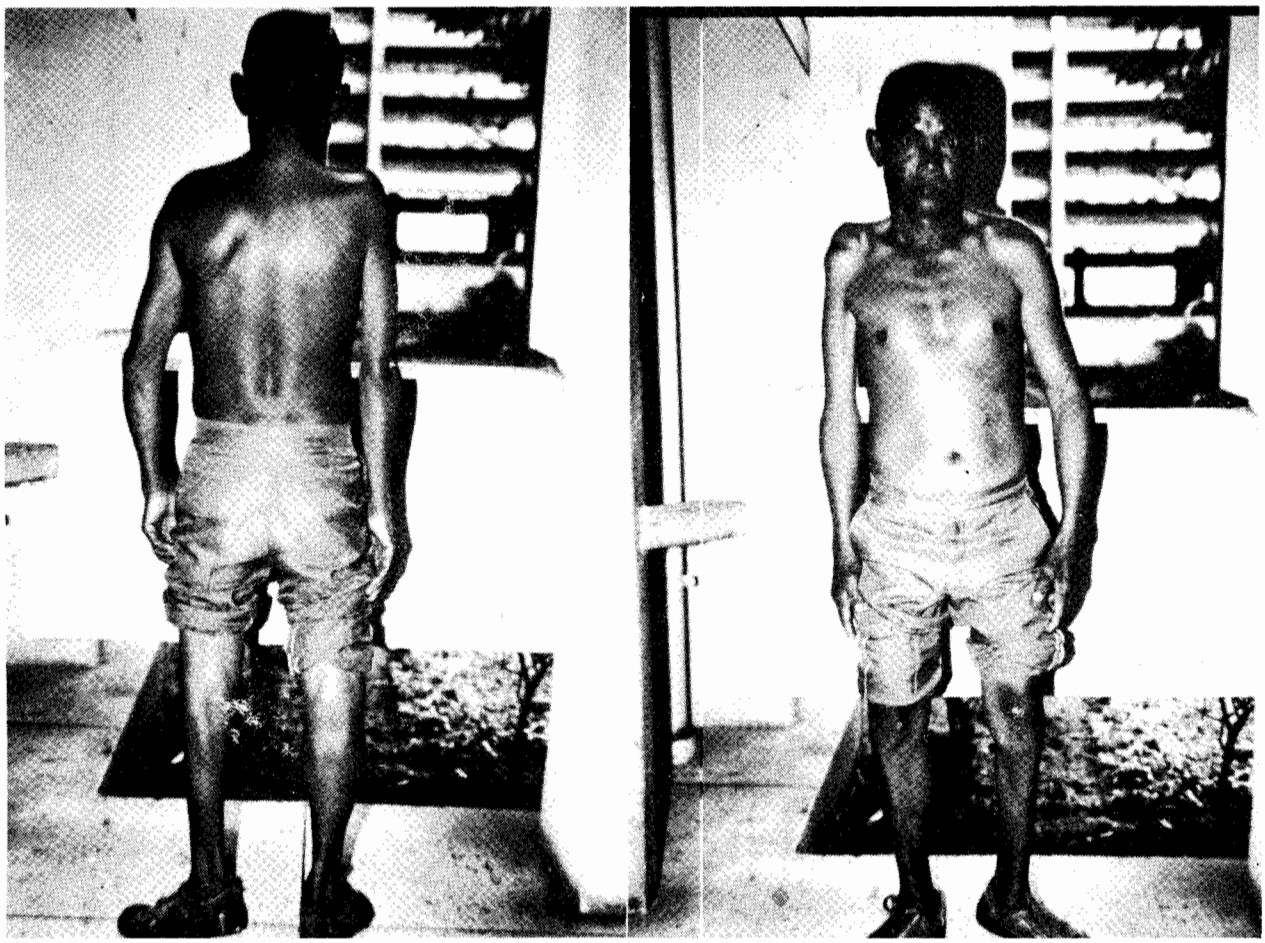
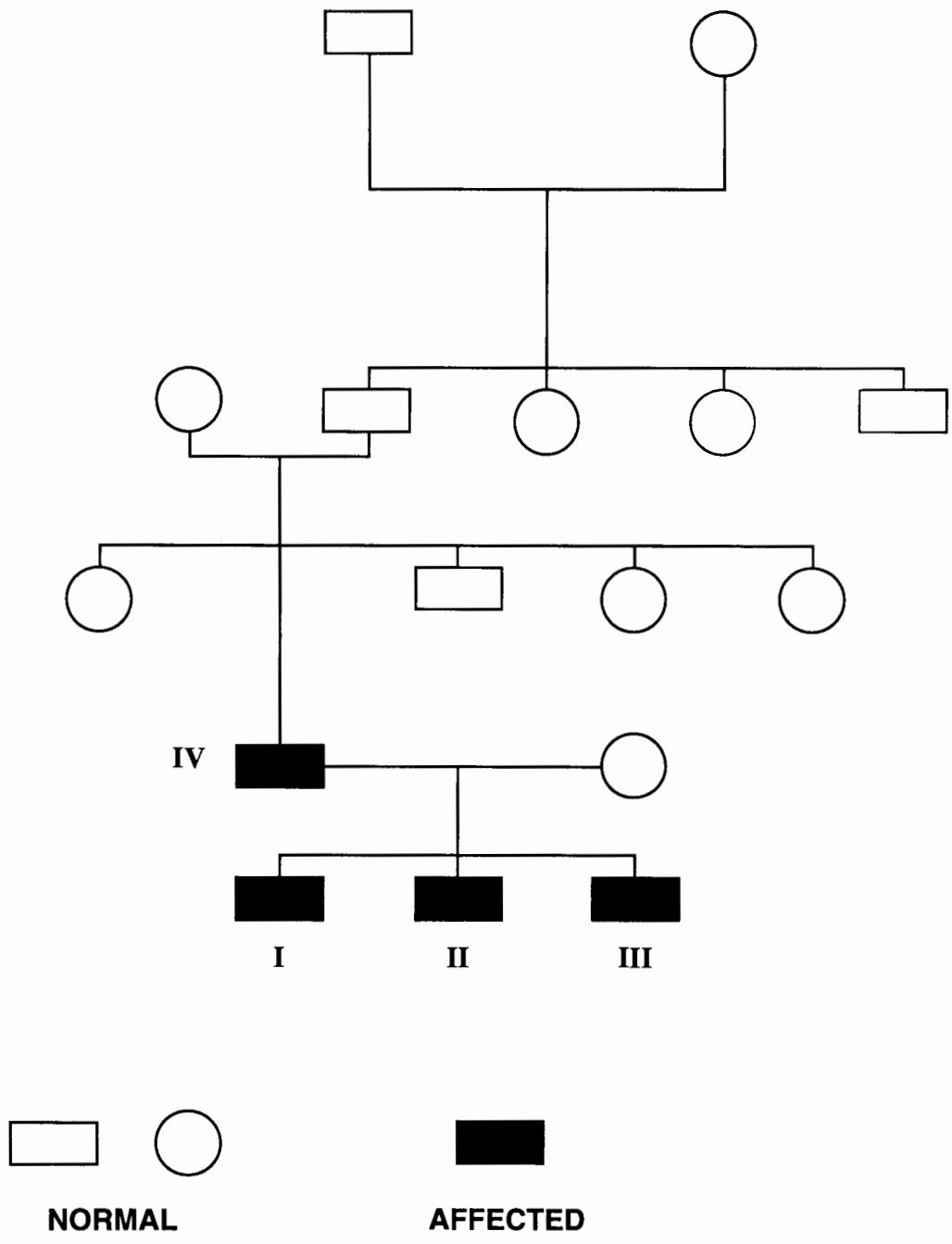


Figure IV showed muscle atrophy of the right shoulder, arm, left scapular area and calf muscles.

Figure V showed pedigree



case number	MNCV	Right					Left				
		distal latency	distance	amplitude	duration	velocity	distal latency	distance	amplitude	duration	velocity
I	Median	5.45	19.2	1.8	14.2	54.8	5.15	19.0	1.3	18.2	54.2
		8.95		1.7	21.0		8.65		1.5	18.0	
	Ulnar	4.9	21.0	2.2	13.7	62.6	4.1	21.3	3.7	12.4	62.6
		8.3		1.88	16.9		7.5		3.6	19.0	
II	Meduian	4.0	20.5	3.3	16.2	44.5	4.1	20.0	4.2	15.5	47.0
		8.6		3.0	16.0		8.3		3.8	14.0	
	Ulnar	3.1	20	4	15	47.6	2.9	22.5	3.8	20.0	48.3
		7.3		4.5	14		7.6		3.5	18.0	
	Posterior	4.95	37	4.5	16.0	43.7	5.35	37	5.5	15.3	37.3
	tibia	13.4		5.0	13.5		15.3		3.8	14.0	
	Common	3.95	29	4.8	12.5	39.1	4.75	36.7	4	9.0	36.7
	Peroneal	11.3		4.5	16.5		12.6		3.5	10.2	
III	Median	4.1	21.5	5	17	39.0	4.5	18.5	5.2	14.8	46.2
		9.6		4.0	12		8.5		4.8	14.2	
	Ulnar	2.75	20.5	5	10	53.9	2.9	19.0	5	14.2	54.2
		6.75		4.5	11		6.4		4.5	13.8	
	Posterior	4.8	34	5.8	14.8	47.2	5.05	35	6	16.6	45.4
	Tibial	12.1		4.9	14.5		12.67		5.5	14.8	
	Common	4.5	27	4.5	16.6	43.9	5.4	24.5	5.0	13.0	44.5
	Peroneal	10.7		5.0	14.0		11.1		4.8	12.5	
IV	Median	2.45	16.5	388 uv	8.9	67.3	3.2	17	6.5	14.0	62.9
		4.90		990 uv	11.8		5.9		7.0	13.5	
	Ulnar	3.55	19.2	5.3	11.8	62.9	3.4	19	8.7	13.9	60.3
		6.60		3.9	12.1		6.5		8.5	13.5	

Table I : Motor nerve conduction findings of study group

Case number	SNCV	Right					Left				
		distal latency	distance	amplitude	duration	velocity	distal latency	distance	amplitude	duration	velocity
I	Median	4.38	19.0	16.2 uv	4.8	48.1	4.1	19.0	12.8 uv	2.7	47.5
		8.33		7.2 uv	4.4		8.1		12.4 uv	2.9	
	Ulanr	3.8	19.8	10.4	3.4	44.0	8.6	21.5	12 uv	2.5	
		8.3		10.0	3.6		10.4		11.8 uv	2.6	48.6
	Sural			No response					No response		
II	Median	3.7	18.6	9.2	2.9	43.2	3.6	19.6	12.0	2.0	40.8
		8.0		3.4	2.7		8.4		8.4	2.1	
	Ulnar	3.4	21.5	7.2	1.5	40.5	3.9	22	15.0	2.6	44.8
		8.7		5.2	2.0		8.8		1.36	2.5	
	Sural			No response					No response		
III	Median	3.08	18	20 uv	13.0	53.7	3.31	16.5	8.5 uv	4.4	52
		6.43		15 uv	10.0		6.48		8.0 uv	4.0	
	Ulnar	2.79	22	20 uv	4.3	53.9	6.81	20	8.5 uv	2.5	51.4
		6.87		17 uv	4.5		10.7		14.0 uv	2.8	
	Sural	3.4	10 cm	10.2	2.4		3.2	10	14 uv	2.8	
		4.2	14 cm	12.6	2.5		4.3	14	10 uv	2.8	
IV	Median	3.7	16.5	75.2 uv	3.8	64.9	4.2	16.5	54.4 uv	3.9	55.5
		6.3		36.2 uv	3.9		7.1		20.6 uv	3.7	
	Ulnar	3.64	16.2	48.0	3.7	57.8	3.7	19.5	29.4 uv	2.7	56.8
		6.44		35.6	3.1		7.1		20.0 uv	3.5	
	Sural	2.7	10 cm	13.5 uv	1.8		3.0	10 cm	26 uv	2.2	
		3.6	14 cm	13.2 uv	1.9		3.9	14 cm	10 uv	2.0	

Table II : Sensory nerve conduction findings of study group

Case number	muscle	insertional activity	spontaneous activity			MUAP			
			fasiculation	fibrillation	positive sharp wave	amplitude	duration	polyphasics	recruitment
I	Ist DI Rt	↑	-	++	++	12.4-21.8	9.8-11.8	↑ small	incomplete
	ECR Rt	↑	-	++	+	11.0-22.6	10-12.5	↑ small	incomplete
II	Deltoid Lt	↑	+	+	+	20-26.3	6.5-8.0	↑ small	incomplete
	ECR Lt	↑	+	++	+	23.8-30.0	6.0-9.5	↑ small	incomplete
III	Deltoid Lt	↑	+	++	+	26.0-29.0	6.5-9.2	↑ small	incomplete
	Ist DI Rt	↑	+	+	+	25.7-28.2	5.9-10.2	↑ small	incomplete
IV	biceps Rt	↑	-	-	-	11-18.9 mv	10-15.0	↑ small	incomplete
	ECR Rt	↑	-	-	-	15.8-28 mv	11-14.8	↑ small	incomplete

Table III : Electromyographic findings of study group