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BENIGN MONOMELIC AMYOTROPHY

A STUDY OF TWENTY-ONE CASES

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ABSTRACT - A consecutive series of 21 patients with single limb atrophy (monomelic amyotrophy) is reported. Sixteen had lower limb atrophy and five had upper limb involvement. The median age of the onset was 20 years. Characteristic features were sporadic occurrence, wasting confined to one limb, insidious onset with slow progression, stabilizing in 1 to 4 years, and absence of pyramidal signs. All the patients with upper limb involvement were male, however in our cases with lower limb amyotrophy there were no male preponderance. We observed wasting of the entire length of the lower limbs in six patients. There were nine cases with amyotrophy restricted to the leg and one with amyotrophy only in the thigh. In the upper limb in four cases the involvement was distal and in one patient the atrophy was proximal. The electromyographic features were suggestive of anterior horn disease not only in the affected limb but also, in some cases, in clinically uninvolved limb. Cervical or lumbar MRI was normal. MRI of the lower limb disclosed increased signal intensity in the gastrocnemius and soleus muscles in one patient suggesting denervation.

KEY WORDS: lower motor neuron, monomelic amyotrophy, spinal muscular atrophy.

Amiotrofia monomélica benigna: estudo de 21 casos

RESUMO - Relatamos uma série consecutiva de 21 pacientes com amiotrofia de um só membro, denominada de amiotrofia monomélica. Em 16 casos a atrofia era no membro inferior e em 5 localizava-se no membro superior. Todos eram jovens e a idade média do início foi 20 anos. Os dados mais característicos da doença foram ausência de história familiar, comprometimento de um só membro, início e progressão lenta estabilizando em até 4 anos e ausência de sinais piramidais. Nossos enfermos com amiotrofia de membro superior eram todos do sexo masculino, entretanto naqueles com amiotrofia do membro inferior havia igualdade de sexos. Dos pacientes com atrofia de membro inferior, em 9 a atrofia era restrita a perna, em 6 era em todo o membro e somente um apresentava amiotrofia localizada só na coxa. Naqueles com comprometimento do membro superior a atrofia era distal em 4 e proximal em 1. Os achados na eletromiografia foram compatíveis com acometimento do II neurônio motor. Todos foram submetidos a RM da coluna cervical ou lombar que se mostrou normal. Em um caso realizamos RM da perna acometida que evidenciou sinais hiperintensos nos músculos gastrocnemius e soleus, o que sugere desnervação.

PALAVRAS-CHAVE: neurônio motor inferior, amiotrofia monomélica, amiotrofia espinhal.

Benign monomelic amyotrophy (BMA) is a rare condition in which neurogenic amyotrophy is restricted either to the upper or to the lower limb[1,2]. BMA is usually sporadic, it has an insidious onset and slow progression followed by stabilization in 2-4 years. It is found mostly in young adults. Most of the cases reported are Japanese, Indian and Malaysian[2,3].

When BMA is restricted to the distal aspect of the upper limb it is called Hirayama disease[4,5]. Hirayama et al.[4], in 1959, entitled this condition juvenile muscular atrophy of unilateral upper

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extremity. Sobue et al.[6] published the largest series of patients with BMA, reporting his findings in 71 patients. Although the cause of this disease remains to be elucidated the electromyographic (EMG) findings suggested that muscle atrophy is due to a degeneration of the lower motor neuron[7]. The relationship with others motor neuron diseases as amyotrophic lateral sclerosis is unclear.

We describe the clinical, EMG, cervical or lumbar magnetic resonance image (MRI) studies of a consecutive series of 21 patients with muscular atrophy confined to an upper or a lower single limb. They were examined and followed-up in the Service of Neurology (Neuromuscular Section) of our university hospital.

REPORT OF CASES

The criteria for labeling a case as MA were as follows: 1) clinical evidence of wasting and weakness confined to one limb (EMG evidence of denervation in another limb was not a reason for exclusion); 2) progressive course, or initial progression followed by stationary course; and no evidence of compression lesion of the spinal cord [1].

During a five years period (from 1995 through 1999) we examined 21 patients with single-limb atrophy. Patients had no history of previous poliomyelitis. All cases were sporadic. The clinical features are summarized in Table 1. There were 13 males and 8 females. Sixteen patients had wasting of one lower extremity and five patients had atrophy of one upper extremity. In the lower extremity the amyotrophy was distal in nine cases

Table 1. Clinical and laboratory features of 21 patients with monomelic amyotrophy.

Patient	Gender	Age of onset-years	Duration of illness-years	Side	Amyotrophy	Tendon reflex	Pes cavus	EMG Denervation	MRI of Spinal cord
1	M	4	2	R	Thigh-Leg	N	-	R Thigh-leg	N
2	M	23	2	R	Forearm-Hand	N	-	R Forearm-hand	N
3	M	28	3	R	Thigh-Leg	A0	+	R Thigh-leg	N
4	F	16	2	L	Leg	P-A0	-	L Leg	N
5	M	19	2	L	Thigh-Leg	N	-	L Thigh-leg	N
6	M	41	3	R	Shoulder-Arm	N	-	R Shoulder-arm	N
7	M	25	4	L	Thigh-Leg	N	-	L Thigh-leg	N
8	F	29	2	L	Leg	N	+	L Leg	N
9	M	20	4	L	Leg	P-A0	+	L Leg	N
10	F	17	3	L	Leg	P-A0	-	L-R Leg	N
11	M	15	3	L	Forearm-Hand	N	-	L Upper/lower limb	N
12	M	30	4	L	Leg	A0	+	L leg	N
13	F	18	3	L	Thigh-Leg	P-A0	-	L Thigh-leg	N
14	M	12	2	L	Thigh	P0	-	L Thigh	N
15	F	19	3	R	Thigh-Leg	A0	+	R Thigh-leg	N
16	F	17	3	L	Leg	A0	-	L Leg	N
17	F	23	2	R	Leg	N	-	L Leg	N
18	M	15	1	L	Forearm-Hand	D0	-	L Forearm-hand	N
19	M	15	2	L	Forearm-Hand	D0	-	L Forearm-hand	N
20	F	18	2	R	Leg	A0	-	R Leg	N
21	M	31	4	L	Leg	A0	+	L Upper/lower limb	N

M, male; F, female; R, right; L, left; N, normal; 0, absent; A, ankle reflex; P, patellar reflex; +, present; -, absent; D,dist al reflex of upper limb; EMG, Electromyography; MRI, Magnetic Resonance Image.

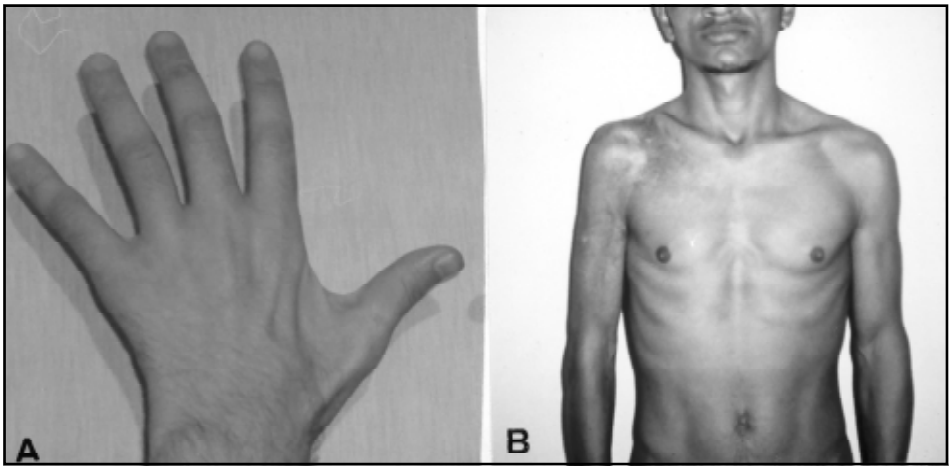

Fig 1. A. Case 11 - Amyotrophy of left hand . B. Case 6 - Wasting of muscles of proximal right limb.

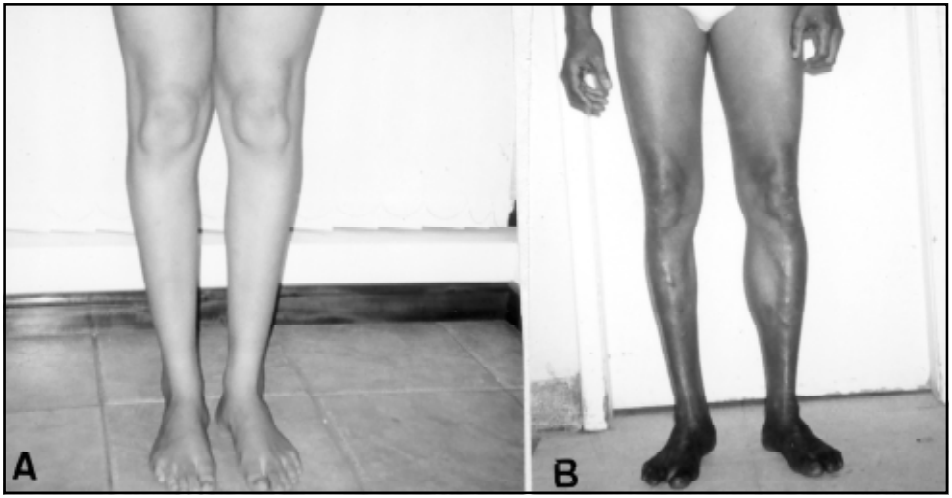

Fig 2. A. Case 20 - Wasting of muscles of right leg. B. Case 3 - Atrophy of right leg and thigh muscles.

proximal in one, and proximal and distal in six cases. In the upper extremity the amyotrophy was proximal in one case and distal in four cases (Figs 1 and 2). Amyotrophy was out of proportion with distal muscle weakness and all patients were still able do walk on their toes. There was no fasciculation. The age of onset ranged from 4 to 41 years, and it was difficult to determine it precisely. The course was slowly progressive, stabilizing in 1-4 years. Unilateral pes cavus was present in 6 cases with lower limb amyotrophy. The ankle reflex was absent in 6 cases. Amyotrophy of lower limb with absent knee and ankle reflexes were seen in 4 cases. In 5 patients with lower limb amyotrophy the patelar and the ankle reflexes were normal. In the patient with proximal lower limb amyotrophy the knee reflex was absent. In two cases with amyotrophy of the upper limb the distal reflexes were absent. Tendon reflexes had normal responses in the case of proximal amyotrophy and in the other two cases of distal upper limb atrophy. Sensory examination was normal.

Motor and sensory conduction studies were performed according standard techniques. Compound muscle and sensory nerve action potential amplitudes, conduction velocities and F-wave response latencies were measured in a conventional fashion. We examined the ulnar, radial, median, peroneal, tibial and sural nerves. All sensory and motor amplitudes, distal and F-latencies and motor and sensory velocities were normal.

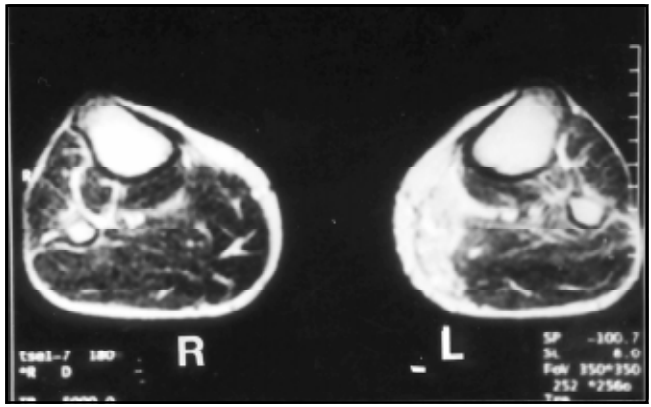

Fig 3. Case 21 - MRI of calf. Note the selective, asymmetrical involvement of left posterior leg muscles (gastrocnemius and soleus muscles). R: right, L: left.

EMG was performed using standard concentric needle electrodes. In atrophic muscles of all patients we found areas of reduced mild spontaneous activity with fibrillation potentials and positive waves, and in some patients fasciculation potentials were recorded. Recruitment was reduced in a similar pattern and motor unit potentials were of moderate to large amplitude and excessively polyphasic. In the unaffected contralateral limb of patient 10 EMG demonstrated evidence of denervation. In patients 11 and 21 the homolateral limb showed findings suggestive of chronic denervation.

Cervical or lumbosacral MRI was performed respectively in patients with upper or lower limb amyotrophy. MRI excluded intraspinal pathologies and root compression in all cases.

Muscle MRI of the atrophic lower limb was performed in patient 21. The T1 and T2 weight images showed increased signal intensities in the soleus and in the lateral and medial gastrocnemius muscle (Fig 3). We did not perform muscle or nerve biopsy in our patients.

DISCUSSION

BMA is a rare condition in which the neurogenic atrophy is restricted to one limb. Since the clinical profiles of patients with atrophy of one upper or lower limb are essentially similar they can be grouped under a single condition designated BMA. Its incidence and prevalence are unknown. A clinical study of 110 cases of motor neuron disease (MND) in eastern India performed by Saha et al.[8], in 1997, showed that BMA encompassed 22.7% of cases. In the series of Gourie-Devie et al.[1] BMA constituted 11% of the MND. Most cases have been described in India and Japan[1-3]. BMA is usually sporadic. Few cases with familiarity have been reported [4,6]. We had no familial cases in our series. The superoxide dismutase (SOD 1) gene was negative in two brothers with BMA studied by Robberecht et al.[9]. Di Guglielmo et al.[10] studied the spinal muscular atrophy (SMA) gene in 7 patients with BMA, indicating that deletions at the gene of SMA are not present in BMA. Paradiso [11], in 1997, suggested a correlation between trauma and/or immobilization in two children with BMA who suffered from fracture of upper and lower limb and were immobilized. However it is unclear whether the prevalence of trauma is greater in patients with BMA than in age-matched controlled population. The pathophysiology of BMA is still unknown.

Nearly 90 per cent of our patients developed symptoms between the ages of 18 and 22 years. There are series ranging from 2 to 30 years[5]. Our youngest patient was 4 years-old and the oldest was 41. The median age of our cases was 20.7 years.

The mean time duration of the disease for all subjects when first seen by us was 2.6 years. The clinical course of this illness is usually progression during 1 to 2 years followed by relative stabilization thereafter[1,4,6,12]. In Peiris et al.[13] long-term study, the disease arrested within 5 years in 75 percent of their patients.

The disorder is virtually confined to males[4,12]. Out of 71 patients studied by Sobue et al.[6] only 12 were female. Gourie-Devie et al.[1] reported 23 cases, 13 with amyotrophy of the upper limbs and 10 of the lower limbs. Only two patients with upper limb atrophy were female. All of our 5 patients with upper limb amyotrophy were male, however in our cases with atrophy of lower limb there were no male preponderance (8 males and 8 females).

In our 4 cases with upper limb wasting, the atrophy was in the hand and forearm. In most reported patients described the wasting and weaknesses were limited to the distal muscles of one upper limb[1,3,4,6,12,13]. Rare cases have been reported with only proximal upper limb amyotrophy[14,15]. Our case number 6, a 46-year-old man, had a severe atrophy and mild weakness of the left shoulder and arm with a slow progressive course (3 years) followed by a seemingly stationary period.

We observed diffuse wasting of the entire lower limb in 6 patients. Atrophy strictly confined to the leg muscles was seen in 9 of our cases. In one patient the amyotrophy was present only in the thigh. Although 10 cases studied by Gurie-Devie et al.[1] were almost similar to ours these authors did not observe a case with amyotrophy restricted to the proximal lower limb. We would like to call attention for this type of proximal presentation in the lower limb, as occurred with our patient number 12 .

In all of our patients chronic neurogenic changes were found during EMG studies, characterized by potentials of increased amplitude, and polyphasic, consistent with the underlying pathophysiologic process of denervation and reinnervation. Fasciculation potentials were recorded in some patients. In a few patients EMG studies revealed neurogenic changes not only in the weak muscles, but also in muscles not clinically affected. Goirie-Devie et al.[1] detected mild denervation in the normal muscles of 3 patients with upper limb amyotrophy. In their 10 cases of lower limb atrophy, 2 patients showed denervation in the contralateral limb. Some authors[1,2,3,13,16] have made similar observations. We have one patient (Case 10) with lower limb amyotrophy in which EMG disclosed evidence of denervation in the contralateral limb. In two patients (Cases 11, 21) there was mild denervation of the limb of the same side.

Imaging studies of the cervical and lumbar cord have shown variable results. Biondi et al. [17] studied 7 patients with distal upper extremity MA. In 3 cases there were focal and unilateral atrophy of the lower cervical cord limited to the anterior horn region. One patient had bilateral anterior atrophy and the last had a round and small cervical cord at C7-T1 levels. The CT myelogram of 5 patients with BMA of distal upper limb described by Oryema et al. [16] showed unilateral wasting of the cervical cord. Di Muzio et al.[18] performed lumbosacral MRI in 6 patients with unilateral lower limb amyotrophy. There were no changes. Several authors have performed cervical or lumbosacral MRI in BMA patients excluding spinal or root pathologies[1,2,15,18]. In all of our cases we performed MRI of the cervical or lumbosacral cord. We did not observe any consistent finding.

Computed tomography (CT) and MRI of skeletal muscles involved can offer useful additional information on muscle involvement in MA[2,7,18,19]. The CT scanning of muscles showed fibroadipous substitution of posterior muscles in the affected leg, but sometimes there was a selective involvement of the gastrocnemius medialis muscle in the clinically unaffected limb[2]. In the 6 cases with CT of lower limb studied by Di Muzio et al[18], gastrocnemius and soleus muscles were the most affected. Only one patient had an attenuation of the gastrocnemius medialis muscle in the clinically unaffected leg. Hamano et al[19] reported 2 patients with BMA of the distal lower limb, in which they performed a MRI of the lower limb. In both the T1- and T2- weight MRI showed increased signal intensities in the semimembranous, semitendinous, vastus intermedius muscles, as well as the soleus and medial gastrocnemius muscles on the affected limb on the right side. In the other case with only leg amyotrophy there were atrophic changes in the soleus, and in lateral and medial gastrocnemius. MRI showed involvement of the soleus and lateral gastrocnemius in our patient number 21. This image suggests lack of muscular tissue due to fibroadipose substitution[18]. Our findings were similar with the recently described by Hamano et al.[19]. As the combination of clinical and electromyographic examinations could not detect mild involvement in deep skeletal muscles, MRI muscle examination is very useful for detecting such affected muscles.

The differential diagnosis of BMA includes illnesses presenting painless weakness and amyotrophy in the upper or lower limb. In distal spinal muscular atrophy the wasting is bilateral and often symmetrical[2,12]. Absent bulbar and pyramidal signs, and lack of spreading to the other limbs after 4 years distinguish BMA from a monomelic onset of amyotrophic lateral sclerosis[2,12]. Serratrice et al.[20] described cases of chronic focal myositis, that resembled BMA. In these cases the elevated serum CPK, the EMG and the muscle histologic findings further differentiate the two conditions. An entity of "late-progression of poliomyelitis" merits comments. In this disease there are: 1) a definite history of poliomyelitis; 2) residual but stable neurologic deficits; 3) a quiescent period of ten years or more. Although there are not new cases of poliomyelitis in Brazil in the last ten years, detailed interrogation and examination failed to reveal any history of poliomyelitis with focal neuromuscular deficit in childhood in our cases[21]. Post-polio syndrome is characterized by a definite history of poliomyelitis with residual and stable amyotrophy and weakness for a period of 10 years followed by progressive loss of strength and muscle atrophy occurring asymmetrically. When the amyotrophy is distally in the upper limb BMA should be distinguished from multiple motor neuropathies. In this disease there is an evidence of conduction block in motor nerves and high titers of anti-GM1 ganglioside antibodies may be found in the serum[12].

In conclusion, we should consider the diagnosis of BMA in cases of slowly progressive unilateral amyotrophy restricted to one limb followed by stabilization, and with neurogenic changes in the EMG. Most patients in our consecutive series are similar to those previously described[1,3,4,6,7,12] . However in our cases the amyotrophy was more common in the lower than the upper limb, and there was no male preponderance in the patients with lower limb amyotrophy.

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