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NON-PROGRESSIVE JUVENILE SPINAL MUSCULAR ATROPHY OF THE DISTAL UPPER LIMB

(HIRAYAMA'S DISEASE)

A CLINICAL VARIANT OF THE BENIGN MONOMELIC AMYOTROPHY

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ABSTRACT - Hirayama's disease (HD) is frequently found in Asia, and is rarely referred among westerners. It affects young people with higher incidence in males. It is a focal distal amyotrophy with unilateral or asymmetric bilateral involvement of C7, C8 and T1 innervated muscles. HD appears sporadically and has a benign evolution with clinical stabilization in around one year. We report four young male patients with clinical and electrophysiological alterations described in HD, which were followed-up during 5 years. Electromyographic findings were indicative of lower motor neuron involvement. We analyzed cervical MRI aiming at understanding if a questionable spinal cord compression could be implicated in the pathogenesis, but no abnormality was verified. In view of its clinical, and EMG characteristics, HD is no more than a benign monomelic amyotrophy (BMA) clinical variant, and not a specific disease. This eponym could be considered only for the distal upper limb variant *(Hirayama's variant)* of the BMA.

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

Atrofia muscular espinhal distal do membro superior não progressiva juvenil (doença de Hirayama): uma variante clínica da amiotrofia monomélica benigna

RESUMO - A doença de Hirayama (DH) é frequentemente encontrada na Ásia, sendo raramente referida entre os ocidentais. Acomete indivíduos jovens, preferencialmente do sexo masculino. Tem início na adolescência, determinando amiotrofia focal distal com envolvimento unilateral, ou bilateral, assimétrico, de músculos inervados por C7, C8 e T1. É enfermidade de aparecimento esporádico, com evolução benigna para a estabilização clínica em torno de um ano. Relatamos quatro pacientes jovens do sexo masculino com alterações clínico-eletrofisiológicas compatíveis com DH, acompanhados durante cinco anos. Os achados eletromiográficos foram compatíveis com o comprometimento do segundo neurônio motor. Analisamos os achados de ressonância magnética da coluna cervical visando conhecer se questionável compressão medular estaria implicada na patogênese, não tendo sido encontrada qualquer anormalidade. Diante de suas características clínicas e eletromiográficas, podemos considerar ser a DH apenas uma variante clínica do grupo das amiotrofias monomélicas benígnas (AMB) e não uma doença específica. Este epônimo poderia ser utilizado apenas como a forma distal do membro superior (*variante de Hirayama*) da AMB.

PALAVRAS-CHAVE: neurônio motor inferior, amiotrofia monomélica, doença de Hirayama, atrofia muscular espinhal.

Hirayama's disease (HD) is the eponym which continues to be used to identify a rare condition frequently reported in Asia, most in Japan and India, and rarely referred among westerners[1-3]. Hirayama et al.[4] called attention for a condition they entitled juvenile muscular atrophy of unilateral upper extremity. It affects young people with higher incidence in males[4,5] . It is a focal distal amyotrophy

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with unilateral or asymmetric bilateral involvement of C7,C8 and T1 innervated muscles[4]. EMG findings are those seen in lower motor neuron involvement[3-5]. HD appears sporadically and has a benign evolution with clinical stabilization in 1-2 years[4,5]. On the other hand, under the diagnosis of benign monomelic amyotrophy (BMA) are described patients in which neurogenic amyotrophy is restricted to the upper or lower limb in their distal or, more rarely, proximal portions[5-12]. In most published series patients have the upper limb more involved, including HD cases[4-6]. In our recent consecutive series of BMA the lower limb was the more involved[13]. In all these series the clinical and electrophysiological aspects are consistent with a benign involvement of the lower motor neuron[5,6,13]. In many cases some EMG findings are also seen in muscles of other segments of a limb or in other limb(s)[3,6].

We describe the clinical, EMG and magnetic resonance image (MRI) findings in four patients with a distal amyotrophy of forearm and hand, discussing the nosological identity of the so called "Hirayama disease".

CASES

Patient 1. This 20-year-old Caucasian boy was evaluated by us three months after he developed atrophy in the intrinsic muscle of his left hand when he was 15-year-old. The weakness was first observed during certain activities such as turning door knobs, opening bottles, and holding small utensils. The weakness worsened over several months stabilizing in around one year. Cramps were not noted during the evolution of his symptoms. Pain, numbness, or dysesthesia in the left upper or other limbs were not referred. His past medical history was unremarkable with no trauma reference. No other family members had neuromuscular complaints (Table 1).

Physical examination revealed normal vital signs. Neurologic examination revealed atrophy of the left hand intrinsic muscles and, to a lesser degree, in the left forearm flexor muscles (Fig 1). The weakness of the intrinsic hand muscles on the left was 3/5 (MRC). Mild weakness was also verified in the *abductor digiti quinti* (ADQ) muscle of the right hand. Strength was normal in the remaining upper limb muscles and in the lower limbs. Fasciculations were absent. Tendon flexor reflex was reduced (1/4) in the left distal upper limb, other reflexes were symmetrically present throughout. There were no sensory, pyramidal tract or bulbar signs. Tremors were not observed.

Routine laboratory tests, including serum creatine kinase, were within normal limits. Motor and sensory conduction studies and electromyographic examination were performed using standard techniques. The motor and sensory conduction velocity examination of the affected limb was normal and similar to the unaffected limbs. F-wave latencies were normal in the affected and in the unaffected limbs. No conduction block was present. The needle examination showed abnormal spontaneous activity at rest (positive sharp waves, fibrillation potencials) with large amplitudes of motor unit potentials (MUPs) in the ADQ, *first dorsal interosseus* (FDI) and

Table 1.Clinical/laboratory features of four patients with Hirayma's variant of benign monomelic amyotrophy.

Patient n°	Age (year)	Gender	Age at onset	Side affected	Approx. period for stabilization (mo.)	Amyotrophy	Tremor	MNC	EMG pattern	MRI
1	20	M	15	L	12	Hand-forearm	A	N	LMN	N
2	23	M	16	R	12	Hand-forearm ("oblique" atrophy)	A	N	LMN	N
3	21	M	15	L	18	Hand-forearm ("oblique" atrophy)	Min	N	LMN	N
4	27	M	23	R	18	Hand-forearm ("oblique" atrophy)	Min	N	LMN	N

MNC, motor nerve conduction study; EMG, needle electromyography; MRI, magnetic resonance image; M, male; R, right; L, left; A, absent; Min, minipolymyoclonus; N, normal; LMN, lower motor neuron involvement.

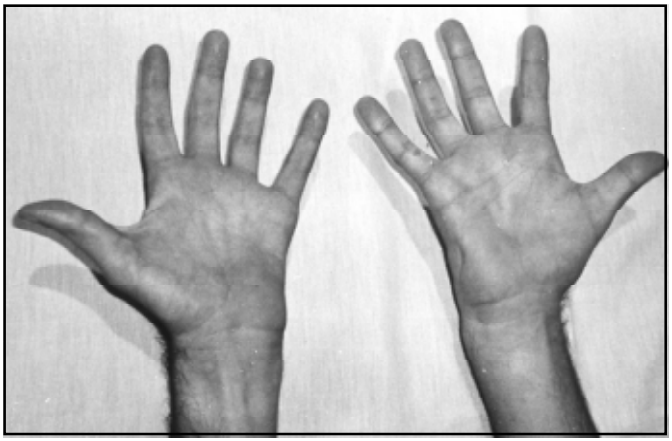

Fig.1. Case 1. Amyotrophy of left hand.

abductor pollicis brevis (APB) muscles in the left hand. There were positive sharp waves (1/3) and fibrillation potentials (1/3) in the ADQ muscle in the right hand (Table 2). A cervical and upper thoracic cord MRI performed in T1 and T2-weighted images showed no abnormalities.

After stabilization of symptoms in one year no second episode of deterioration was noted during the five year this patient was followed up.

Patient 2. This 23-year-old right-handed Caucasian man developed slowly progressive distal weakness and atrophy of the right hand and forearm at the age of 16 years when he was referred to us. These symptoms stabilized in approximately one year. Sensory symptoms or cramps were not referred previously or during the follow-up period. No noticeable trauma, exposure to toxins, history of poliomyelitis was present. There was no family history.

Table 2. Abnormal finding in the needle electromyography in the four limbs.

Patient	Muscle tested	Fibrillations/ Positive sharp waves	Fasciculations	Large amplitude of MUPs (giant)
1	L ADQ	2/3+	0	↑A
	R ADQ	1/3+	0	0
	L FDIh	3/3+	1+	↑A
	L APB	1/3+	0	↑A
2	R ADQ	2/3+	0	↑A
	R FDIh	2/3+	0	↑A
	R APB	1/3+	0	0
	R EDC	1/3+	0	0
	R ant TIB	1/3+	0	0
3	L ADQ	1/3 +	0	↑A
	L FDIh	2/3+	0	↑A
	L APB	2/3+	0	↑A
4	R ADQ	2/3+	0	↑A
	R FDIh	1/3+	0	↑A
	R APB	1/3+	0	0

MUPs, motor unit potentials; R, right; L, left; ADQ, abductor digiti quinti muscle; FDIh, First dorsal interosseus muscle, hand; APB, abductor pollicis brevis muscle; EDC, extensor digitorum communis muscle; ant TIB, anterior tibial muscle; ↑A, increased amplitude

Neurologic examination after stabilization of symptoms and during the follow-up revealed atrophy of the muscle of the right forearm and intrinsic muscle of the right hand. Atrophy was evident in the hypothenar muscles more than that observed in the thenar ones. No fasciculations were observed. Strength in the right arm was abnormally rated for the flexion of the wrist (4/5), for the flexion of the second and third fingers (3/5), for the flexion of the fourth and fifth fingers (2/5), and for the flexion of the thumb (3/5). The strength in the other muscles and extremities was normal. Reflexes were preserved and the great toes were flexor on plantar stimulation. Sensory examination and cranial nerves were normal. There was no tremor in the upper extremities (Table 1).

His serum creatine kinase and other routine laboratory tests were normal in the several occasions they were performed. Nerve conduction studies did not disclosed abnormalities, including prolonged F-wave latencies or conduction blocks. The electromyography revealed fibrillation potentials, positive sharp waves and increased amplitude of MUPs in APB, FDI, ADQ, *extensor digitorum* and *anterior tibial* muscles in the right side. T1 and T2-weighted images on MRI of the cervical spinal cord were absolutely normal for his age (Table 2).

In spite of the compromise of his right hand for fine abilities the patient has no restriction for their activities and is working as a seller in a shopping center.

Patient 3. This 21-year-old right-handed Caucasian man was first examined when he was 15-year old. In that occasion he complained of a 4-6 months duration of progressive weakness in his left hand. He observed some difficulty in holding small objects as, for example, a pencil. The weakness slowly worsened during a year and it stabilized in around 18 months. He had no pain, numbness, paresthesia or cramps. There was no history of trauma to the cervical spine, exposure to toxins or insecticides, poliomyelitis, electric shock or other disease. There was no history of similar disease in his family.

Physical examination revealed an age-appropriate teenage with normal vital signs. Neurological examination revealed decreased strength in the intrinsic muscles of the left hand (3/5) with atrophy mainly of the interosseus and hypothenar muscles. Strength of forearm extensor muscles was 4/5. Thenar muscles were mildly atrophic. Tendon reflexes were normal in the four limbs, except the left flexor of the wrist which it was decreased (1/4). Plantar response was in flexion. Both deep and superficial sensations were normal. Cranial nerves were normal. A mild, irregular and jerky tremor was noted in the compromised hand (Table 1).

The blood routine laboratory tests including aldolase and creatine phosphokinase were normal. The motor and sensory nerve conduction studies of the affected and the unaffected limbs were normal. No conduction block was observed. Electromyographic examination showed giant MUPs, and positive sharp-waves and fibrillations at rest in the left FDI, APB and ADQ muscles. Electromyographic examination of the other limbs was normal (Table 2). Cerebrospinal fluid examination was normal. A cervical cord MRI did not show abnormalities.

Patient 4. This 27-year-old melanodermic right-handed man was referred four years ago for evaluation of a right distal upper limb weakness. He first noted difficulty in turning door knobs and opening some utensils. These symptoms progressed slowly, reaching stabilization in 18 months without a severe compromise of his job. Past medical history had no remarkable incidences. There was no similar cases or history of neuromuscular disease in his family.

His general physical examination was normal. Neurologic examination revealed a prominent atrophy of his right forearm flexor muscles and intrinsic hand muscles. There was no fasciculations. Tone was reduced in the right upper limb. Strength was reduced in the ulnar flexor of the wrist (4/5), wrist extensors (4/5) and, most prominently, in the thumb abductors (3/5) and right hand interosseous (2/5) muscles. Tendon reflexes as well as sensation examination were normal in the involved and in the uninvolved limbs. Cranial nerves were normal. A fine, irregular and jerky tremor of the fingers in the right hand was observed (Table 1).

Routine laboratory investigations revealed no abnormalities. Cerebrospinal fluid analysis was within normal limits. The findings of motor and sensory nerve conduction studies were normal, without conduction blocks. The electromyographic findings were consistent with chronic partial denervation (fibrilation potentials, positive sharp-waves, and giant MUPs) recorded in the right APB, FDI and ADQ (Table 2). MRI examination of the cervical spinal cord showed no abnormality.

The patient is still working in a mattress factory.

DISCUSSION

The clinical and electrophysiological findings, and the benign course and good prognosis in our four patients are consistent with the diagnosis of non-progressive juvenile spinal muscular atrophy of the distal upper limb, a condition first delineated in 1959 by Hirayama et al.[4]. The so called Hirayama disease is clinically characterized by juvenile male occurrence, insidious onset, and

unilateral muscular atrophy in the hand and forearm[3-6]. The weakness and muscular atrophy progress for 1 to 3 years before stabilizing over a sufficient period to underline its benignity[4,5,6,13]. It is a rare condition[3,6,14]. Most cases were initially described in India and Japan but several cases have been reported in Western countries[7,8,12,15,16]. We have recently reviewed our series of 21 cases of different clinical presentations of benign monomelic amyotrophy, the first from South America, including the four cases of this report[13]. Reviewing 375 cases of typical focal amyotrophy of upper limb in Western literature Robberecht et al.[2], in 1997, found that the age of onset in 94% of the cases were between 15 and 25 years. Only 10.7% of the 375 patients were female. In about 37% of the revised cases there was atrophy on both sides, although it was almost always markedly asymmetric, as occurried in our Patient 1. This condition is usually sporadic[2,13]. Familial occurrence of HD is very rare[4,5]. In the large series of 71 cases of "juvenile type of distal and segmental muscular atrophy of upper extremities" described by Sobue et al.[5], in 1978, they found only a father and a son with this disease. Superoxide dismutase (SOD1) gene abnormality was not detected in two brothers with focal amyotrophy of the upper extremity, which underlie some forms of familial amyotrophic lateral sclerosis (ALS)[2].

The hallmark of this condition is the atrophy and weakness of the intrinsic muscle of hand and the flexors of forearm with relative sparing of the brachioradialis muscle giving the impression of an "oblique" atrophy[2,17]. The deep tendon reflexes of the affected arm may be normal or hypoactive[2,4,5]. Signs of upper motor neuron involvement and sensory compromise are absent[3,5,6]. An increment of weakness during exposure to cold temperature has been referred in approximately 22% of patients[3,5,6,16]. A distal irregular jerky tremor, also observed in spinal muscular atrophy (*minipolymyoclonus*[18]), was observed in the upper limb of the majority of BMA cases[6]. Muscles innervated by cranial nerves are spared[6,13]. There are rare cases in which the weakness and atrophy occurs in the proximal upper[11-13] or lower limb[13], or in distal lower limb[6,13], or only in the calf muscle[6], demonstrating a variable pattern of the clinical presentation of this condition. In our recent series there were examples of these different presentation forms of BMA[13].

Nerve conduction studies are usually normal[3,5,6,13,16]. Positive sharp waves, fibrillations, and mainly large MUPs are seen on most electromyography performed in these patients [3,6,13]. The presence of large MUPs is consistent with the underlying pathophysiologic process of denervation and reinnervation[5,16]. Similar abnormalities can be found in uninvolved or less-affected limbs in the upper and lower limbs[3,5]. A type grouping atrophy was seen in a few muscle biopsy studies, confirming an underlying neurogenic pathogenesis[2,5,16].

Routine blood laboratory tests and CSF analysis are often normal[3]. The pathogenesis of these focal spinal amyotrophies is unknown[2]. It has been suggested that it may be caused by ischemia at C5 to T1 levels of the spinal cord due to previous trauma or vigorous exercise or excessive neck flexions. Several observations argue against this pathogenic possibility[1,2,3,19]. In the only one autopsy study there was no ischemic lesions in the cervical cord, and no vascular abnormalities[20]. There was only a focal cervical "poliopathy" in the anterior horns of the spinal cord at C5 approximately T1, in a patient who died of lung cancer at the age of 38, 23 years after the onset of the disorder[20].

Computed tomography and myelography or MRI imaging studies of the cervical spinal cord were unable to demonstrate an intramedullary damage[1,2,3,19]. Cervical cord atrophy without a convincing pathogenic relationship has been reported[19]. The compromise of anterior spinal artery blood flow, and consequent anterior horn lesion is not sustained in our MRI studies.

The clinical and electromyographic findings in our cases point to a selective involvement of the anterior horn cells in the lower cervical cord, in the context of a motor neuron disease (MND). MND involving the upper and/or the lower motor neurons, are a heterogeneous group of syndromes with various clinical presentations, most with poor prognosis. In contrast there is a group of condition with a good prognosis involving the anterior horn cells which affects only one or affects one limb disproportionally more than the other known as monomelic amyotrophy (MA)[3,6]. Gouri-Devi et al.[6] reported that MA represented 11% of the patients referred to them with lower motor neuron disease

and can involve the upper or lower limbs. As we can see, depending on the clinical presentation, there are many synonyms to describe this benign group of MND, as referred by Donofrio[3]: monomelic atrophy, benign monomelic amyotrophy, benign focal atrophy, benign focal amyotrophy, benign juvenile focal muscular atrophy of upper extremities, benign monomelic amyotrophy of lower limb, distal amyotrophy of predominantly the upper limbs, juvenile segmental muscular atrophy, juvenile type of distal and segmental atrophy of upper extremities, juvenile muscular atrophy of unilateral upper extremity (Hirayama's disease), juvenile nonprogressive muscular atrophy localized in the hand and forearm, proximal monomelic amyotrophy of the upper limb, and others.

Billé-Turc et al.[17], in 1996, pointed the question if HD is properly a disease or a syndrome, describing 4 cases. However, there were some evident differences from HD in 3 of these cases: presence of antigangliosides antibodies in 1 case, cryoglobulinemia in another case developing bilaterally, and conduction block in a third case. We believe that the eponym Hirayama is not justified for a "syndrome" characterized by distal "oblique" upper limb atrophy, as reported by these authors.

In conclusion, it seems that the nosological identity of HD as a separate disease is actually no more supported by clinical, electrophysiological and MRI evidences that it is no more than one of the different clinical presentations of BMA or MA. We could consider this eponym merely for the clinical presentation variant of distal upper limb observed in the BMA group - *Hirayama's variant* or *form* of BMA.

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