Journal of Neurological Sciences [Turkish] **32:(3)**# 45; 558-565, 2015
http://www.jns.dergisi.org/text.php3?id=913
Research Article

Monomelic Amyotrophy (Hirayama Disease): Clinical Findings, EMG Characteristics and Differential Diagnosis

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Summary

Introduction and Objective: Monomelic amyotrophy (MA) is a benign motor neuron disease with a stationary stage after a progressive course, involving one or more myotomes in the upper limb. In the early stages, it may be difficult to discriminate the diseases presenting with similar clinical course. We reviewed clinical and EMG characteristics and differential diagnosis of MA for this purpose.
Methods: Fourteen cases admitted to the Neurophysiology EMG laboratory of Medical School of Ege University, and diagnosed as having monomelic amytrophy between 2005 and 2014, were evaluated retrospectively along with complaints, age at onset, gender, the involved myotome, EMG and clinical characteristics. Cases with possible etiological diagnoses that might cause mononeuropathy or detected motor conduction block or developed ALS during follow-ups were excluded from the study.
Results: All fourteen patients had onset in the upper limb. The female to male ratio was 4:10, the mean age of the onset was 24±8.64 years (mean ± Standard deviation), minimum-maximum age of onset was 16-40 years, with median value being 21. C8-T1 segments were involved in all cases except one. Follow-up EMG studies demonstrated denervation, fasciculations, and reduced compound muscle action potential amplitudes. Electrophysiologically, our three asymptomatic cases had moderate involvement in the contralateral limb without any complaints.
Conclusion: Cases with MA can be distinguished from ALS by symptom onset at younger ages in men, its benign course and generally with stabilization of clinical and EMG findings in 2 to 4 years. Asymptomatic side should also be considered to be affected electrophysiologically.

Key words: Monomelic amyotrophy, Hirayama disease, Motor neuron disease, EMG, Electrophysiology, Juvenile muscular atrophy

Monomelik Amyotrofi (Hirayama Hastalığı) : Klinik Bulgular, EMG Özellikleri ve Ayırıcı Tanı

Özet

Giriş ve Amaç: Monomelik amyotrofi (MA) üst ekstremitede bir veya birkaç myotomal tutuluşla giden ve bir süre sonra progresyonu duran benign motor nöron hastalığıdır. Semptom ve bulguların başlangıcında, benzer tabloyla seyredebilen hastalıklarla ayırımı yapmak zor olabilmektedir. Bu amaçla MA'nin klinik-EMG özellikleri ve ayırıcı tanılarını gözden geçirdik.
Gereç ve Yöntem: 2005-2014 yılları içerisinde, Ege Üniversitesi Nörofizyoloji EMG laboratuvarına müracaat eden ve monomelik amyotrofi tanısı alan 14 olgu; yakınma, başlama yaşı, cinsiyet, tutulan myotom, EMG ve klinik özellikleri ile birlikte retrospektif

değerlendirilmiştir. Takiplerde ALS gelişen, motor ileti bloğu saptanan veya mononöropatilere neden olabilecek olası etyolojik tanılı olgular çalışmaya alınmamıştır.
Bulgular: On dört olgunun tümü üst ekstremite başlangıçlıydı. Kadın/ Erkek oranı 4/10, yakınmaların başlama yaşı ortalama 24±8.64 (ortalama ± standart sapma), minimum-maksimum başlangıç yaşı 16-40 yaş, ortanca değeri ise 21 idi. Bir olgu hariç tüm olgularda C8-T1 segmenti tutulmuştu. EMG takiplerinde denervasyon, fasikulasyon ve birleşik kas aksiyon potansiyel amplitudlerinde küçülme gözlenmiştir. Karşı ekstremitede yakınması olmayan asemptomatik üç olgumuzda elektrofizyolojik olarak ılımlı etkilenme bulguları saptanmıştır.
Sonuç: MA' lı olgular, ALS'den, daha genç yaş erkeklerde başlaması, benign seyirli olması ve genelde 2-4 yıl içerisinde stabil klinik ve EMG bulgularıyla seyretmesi ile ayırt edilebilir. Asemptomatik görülen tarafta elektrofizyolojik olarak etkilenmiş olabileceği düşünülmeli.

Anahtar Kelimeler: Monomelik amyotrofi, Hirayama hastalıgı, Motor nöron hastaligi, EMG, Elektrofizyoloji, Juvenil muskuler atrofi

INTRODUCTION

Monomelic amyotrophy (MA) is a benign motor neuron disease characterized by atrophy of the upper limbs and muscle weakness restricted to one or several myotomes[4,24]. The disease was first described by Hirayama in 1959 in Japanese cases with atrophy of the distal upper limb[12,13]. The incidenceis higher in Asian countries. MA is also known as Hirayama disease (HH), benign focal amyotrophy etc. Generally the age of onset is 15-25 years[7,11,22]. It affects males 2-3 times more often than females[7,11]. Right upper limb is more frequently affected than the left. Weakness in the contralateral limb may also develop in about 50% of the cases[10,18,22]. The most common finding is the atrophy of the intrinsic hand muscles due to the involvement of C8-T1 segment with sparing of brachioradialis and proximal muscles of upper limb innervated by C5-6 myotomes. Occasionally, it may be associated with proximal upper limb involvement[4]. Weakness may be accompanied by tremor. Tremor has coarse, arrhythmic character[7]. Atypical cases with lower limb onset have also been reported rarely[6,21]. Pathophysiologyis not known exactly. Some studies note that microtraumas and mechanical pressure of the spinal cord and dural vascular structures in the cervical region with neck flexion might play a role[1,3,5,8,9,15,28]. Avoidance of neck flexion and surgical approaches have been reported as the treatment of the disease[20,23].

MATERIAL AND METHODS

Fourteen cases, admitted to our neurophysiology laboratory and diagnosed according to the monomelic amyotrophy criteria modified by Tashiro et al. between 2005 and 2014, were enrolled in the study[24,26]. The cases were informed on the procedures to be done by giving previously prepared written documents and EMG was carried out after they had given written consent. Cases were assessed by history, neurological examination, age of onset of first symptoms, gender, involved myotome, EMG and clinical characteristics. EMG's were performed using Medelec and NicoletViking machines. Motor and sensory nerve conduction velocities and CMAP/DSAP amplitudes of median and ulnar nerves were measured in the upper limb. Motor conduction velocities and CMAP amplitudes of posterior tibial and fibular nerves as well as conduction velocity and amplitude of sensory sural nerve were measured in the lower limb. Muscles of at least 3 regions (spinal segments and / or cranial nerve innervated), including at least one of the upper limbs, were included in the study during needle EMG. In order to

eliminate the motor conduction block, it was searched on the side of weakness.

Exclusion criteria:

• Patients who developed widespread motor neuron disease (ALS) during needle EMG at follow-ups.

• Patients with pyramidal signs at baseline or during follow-up period.

• Patients with motor conduction blocks.

• Patients with a history of poliomyelitis.

• Patients with the diagnosis of Diabetes Mellitus

• Patients with the diagnosis of Vasculitis or positive markers associated with vasculitis (such as ANCA-P, ANCA-C) in tests.

• Patients with abnormal sensory nerve conduction studies or polyneuropathy.

• Patients with the pathology on the cervical MRI (such as syringomiyelia, spinal cord tumors, multiple radiculopathy) that explains the clinical picture, were not included in the study.

RESULTS

Painless weakness followed by atrophy in the upper limbs was present in all of 14 patients. None of the cases had sensorial loss or other complaints. The female to male ratio was 4:10, the mean age of onset was 24±8,64 years (mean ± Standard deviation), minimum-maximum age of onset was 16-40 years, the median value was 21. Seventy nine per cent of our cases showed age distribution in the 15-25 age group (The age distributionis shown in Figure 1).C8-T1 segments were involved in all cases except one (Figure 2). Our case with the latest-onset was 40 years old. MEP was done in 6 cases and the central motor conduction time was normal. Tremor was observed in 3 cases and all of them were men. If we summarize the EMG findings of our cases with the diagnosis of MA: The segmental anterior horn motor neuron involvement signs including frequently C8-T1; denervation, fasciculations, chronic neurogenic MUAP changes, MUAP loss and reduced CMAP amplitudes of motor nerves were observed, where as sensory nerve conduction studies were normal (some EMG characteristics are given in Table-1).

The patients were followed for periods of 7 months to 8 years. Three patients were followed for less than 2 years (7 months, 16 months).It was learned by phone that their progression had stopped and their neurological status was stable because these 3 patients did not come to the control visits for approximately 2 years. The remaining 11 patients'follow-up durations were more than 2 years. The remaining 11 patients had a follow-up duration for more than 2 years. Two patients other than 14 patients began with MA-like findings and developed ALS at their clinical and EMG follow-ups. Age of both patients was above 40 (47 and 48 years old) and both of them were men. Further radiological evaluation is required for possible cervical spinal pathology. The cervical imagesin the neutral position were normal in our cases except one case (Figure 3a-3b).

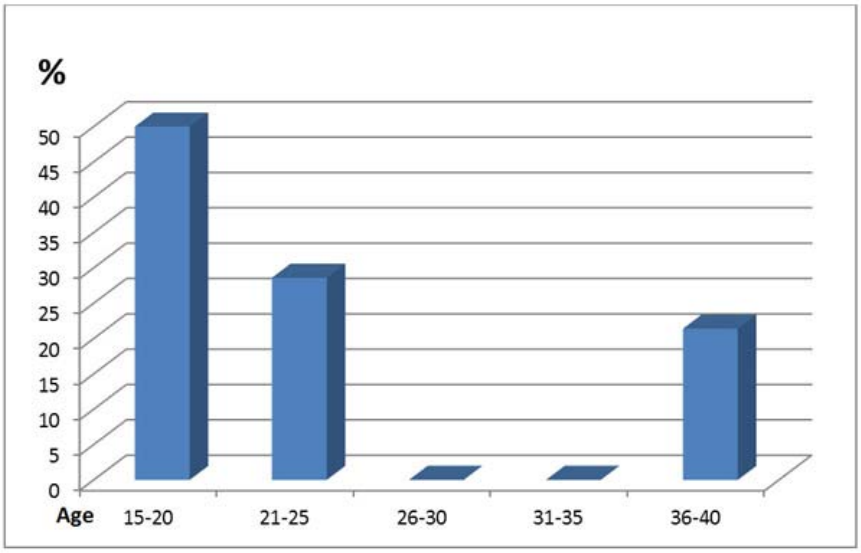

Figure 1: *Age distribution of MA patients.*

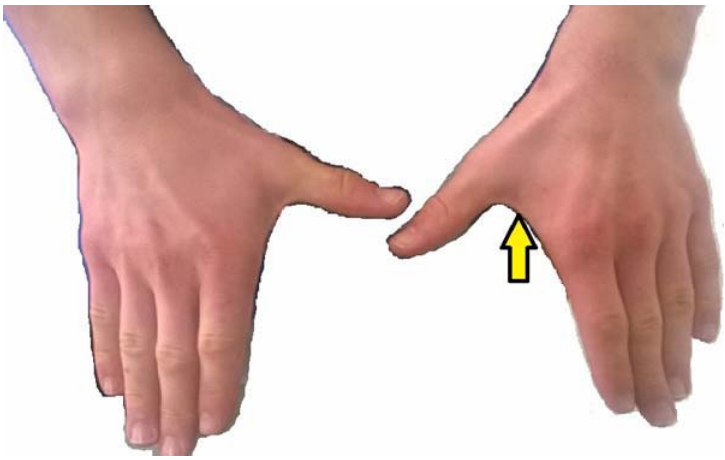

Figure 2: *A case with first dorsal interosseous muscle atrophy.*

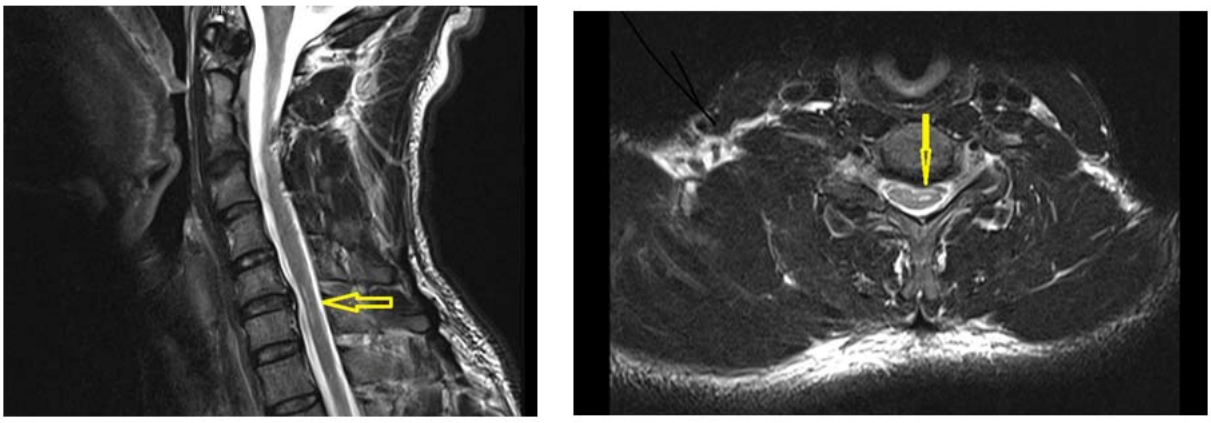

Figure 3: *Hyperintense appearance of the spinal cord of the case with MA on T2-weighted MRI images at the C5-C6 level.(A and B)*

Table1: EMG characteristics of male and female patients with MA.

n:14 %	Affected Side			Affected Segments				
	Right	Left	Bilateral	Prox (C5-6)	Distal (C8-T1)	Prox+Distal (C5-T1)	Denervation	Fasciculation
Male	7,1	14,3	50	0	57,1	14.3	57,1	42,9
Female	21,5	0	7,1	7,1	14,3	7,1	21,5	7,1
Total	28,6	14,3	57,1	7,1	71,4	21,4	78,6	50

DISCUSSION

Although the etiopathogenesis of MA is unknown, many factorsas in ALS are thought to play a role in the pathogenesis. Unlike ALS, it is noted that recurrent neck flexion and chronic compression due to congestion of dural vascular structures may play a role in etiopathogenesis[3,5,8,9,15,28]. While cervical MRIs taken in flexion position for this purpose confirmed this hypothesis in some cases, they were normal in others[3,8,9,15]. Cervical MR images in flexion position were obtained only in one of our cases. In other cases, standard cervical MRI taken in neutral position was normal. A limitation of the present study was that it didn't have contrast-enhanced cervical MRI taken in neutral and flexion positions. According to Kikuchi, MA develops as a result of disproportional growth of dura mater and the vertebral column[15]. In some studies, in MA C5-C7 segments are stated to be involved more commonly in the western countries where as C7-T1 segment in Asiaand Far East[4]. C7-T1 segment involvement was mostly seen in our cases as Hirayama had described. At present, it is still unknown for what reason the disease begins and limits it self. No cause in the pathophysiologyof MA such as microtraumas in the form of repetitive flexion-extension or vascular etiology or other identified reasons was able to explain the occurrence of MA more frequently in men and dominant hand[3,8,9,15,28]. Although symptoms and neurological examination of our 3 patients were unilateral, moderate signs of neurogenic involvement were observed in the electrophysiological studies of the contrlateral limb. The majority of the MA patients were between the 15 and 25 years old. Much morerarely, MA has also been reported in younger (pediatric) and older ages[21,27]. Can being more flexible of the vertebral column in the cervical region in juvenile age, in consequence of loss of this flexibility in the vertebral column in the cervical region with the age due to degenerative changes lead to the cessation of micro-trauma? We have nodata to support this. Genetic defects have been identified in some sporadic and familial cases with MA very rarely[2,19]. It is possible that these genetic defects may facilitate local degeneration of the anterior horn motor neurons in the cervical region.

Differential diagnosis between MA and ALS

Our two cases have presented with asymmetric weakness and atrophy in upper limb as MA at the beginning and widespread anterior horn motor neuron involvement was observed in the follow-ups and these cases were not included in the study. It is important to distinguish whether the neurogenic involvement at EMG is focal or widespread, in order to make distinction between MA and ALS in cases presenting with MA signs[7,14,22,25]. ALS can be differentiated by the spread of the progression to other limbs and cranial muscles, addition of pyramidal signs as well as instability of neurological clinic signs. In other words, absence of bulbar involvement and pathological reflexes, having a benign course and dominancy of young men in MA are important in differential diagnosis[7,14,22]. Enhancement of the space between the posterior dural

sac and subjacent lamina on cervical MRI particularly in neutral position, anterior shifting of posterior dural sac on cervical MRI taken during flexion, presence of the contrat-enhanced epidural component in the same region and appearance of dilated venous structures are considered as signs supporting MA.[3,28]

Differential diagnosis between MA and Cervical spondylotic myelopathy (CSM)

Mostly, cervical spinal MRI may be sufficient alone for the diagnosis of CSM[3,14,22,28]. Cervical spinal stenosis, multiple disc and vertebrae degeneration as well as hyperintense spinal cord signal on T2-weighted sequences on cervical spinal MRI may be observed. MRI findings described above are not observed in MA. Cases with MA are the young male patients whereas cases are the ones with more advanced age in CSM. Weakness in the lower limbs, difficulty in walking, increase in DTR in the lower limbs and Babinski reflex may be seen in severe CSM cases. Hypoesthesia in the lower limbs and even incontinence can be observed in some cases. Electrophysiologically, chronic neurogenic MUAP changescan be observed in both upper limbs, but EMG is normal in lower limb unless there is a lumbar spinal pathology. Motor evoked potential (MEP) studies may reveal prolonged central motor conduction time particularly in the lower limbs. Somatosensory evoked potentials (SEP) are usually lost in the lower limbs.[7,14,22]. Studies are available, however showing that SEP and MEP responses may also be pathological in MA[1].

Differential diagnosis between MA and Cervicalspinal mass

The mass may be shown on pre-and post-contrast MRI of the cervical spine. Clinical findings, varying depending on location of the mass, may be loss of sensation, motor loss and pain in the lower or upper limbs[16]. Mostly,electrophysiological examinationis not necessary in these cases. MA should not be considered in cases with pain and loss of sensation.

Differential diagnosis between MA and syringomyelia

Syringomyelia generally tends to involve the central region of the cervical cord. Some times, it can affect anterior horn motor neuron by extending anteriorly and laterally. The atrophy of intrinsic hand muscles may develop in such a case. Sensory impairment can be observed. As in CSM, pyramidal signs may be also seen in lower limbs in syringomyelia. If syringomyelia is not associated with the spinal cord mass, the progression is slower than MA[7,14,22]. It is diagnosed by showing syringomyelia on the cervical spinal MRI[7,14,22,28]. Major electrodiagnostic findings are: reduced CMAP amplitude, moderate reduction in motor nerve conduction velocity, sparing of the sensory nerve conduction, chronic neurogenic MUAP changes and moderate loss of MUAP in the upper limbs. Deceleration of SSEP and MEP conduction in lower limbs may be determined. However, electrophysiological studies are not usually necessary[1,7,14].

Differential diagnosis between MA and Thoracic Outlet Syndrome (TOS)

The lower trunk of the brachial plexus passing between scalenus muscles and first rib, chronic, recurrent compression-microtraumas are responsible in TOS[7]. Unlike MA, approximately 80% of the patients with TOS are female. Hypoesthesia of medial forearm and hand is commonly present in TOS cases. Weakness and atrophy of intrinsic hand muscles are also seen in TOS as in MA. Although Adson and similar tests are not specific for TOS, the positive results are evaluated in favor of TOS. Reduction or loss of DAP amplitudes of ulnar and medial antebrachial cutaneous sensory nerve in TOS are important for differential diagnosis[7,11]. Other EMG findings of TOS are reduction of CMAP amplitudes of median and ulnar nerves, chronic partial

denervation in C8-T1 innervated muscles, chronic neurogenic MUAP changes, and decreased MUAP firing. Ulnar SEP may be found abnormal in the affected upper limb[7,11,14,22]. Aberrant cervical costae may be determined during radiological investigations performed for TOS.

Differential diagnosis between MA and Multifocalmotor neuropathy (MMN)

In EMG performed to distinguish MA from MMN: Detection of proximal conduction block in motor nerve conduction studies, existence of neurogenic deficit in single nerve area initially, positive anti-GM1 antibody are considered in favor of MMN[7,17,22].

Differential diagnosis between MA and post-polio syndrome (PPS)

Cases with PPS have a previous history of polio. Slowly progresive weakness following the stationary stage for at least 10-15 years develops. Weakness may develop in muscles in which weakness was present previously as well as in new muscle groups. Because the weakness is limited only to the upper limbs, it can be confused with MA, but detailed history may be sufficient. Rarely, weakness may be observed in the cranially innervated muscles in PPS. PPS is diagnosed by clinical findings and the history. PPS may be diagnosed without electrophysiological studies, but electrophysiological studies may be helpful in differential diagnosis. Giant MUAP's are observed in affected muscles in acute polio in pediatric period of PPS while giant MUAP's are not seen in needle EMG in early weakness period of MA. Rarely, interlimb reflex responses can be achieved in PPS, this reflex can not be observed in MA[7,14,22].

CONCLUSION

The diagnosis of MA should always be considered in males between 15 and 25 years old presenting with unilateral painless weakness in the upper limbs. Although there is no complaint in the contralateral upper limb, EMG findings can be detectedin asymptomatic individuals. With regard to the differential diagnosis, cervical screening with MRI, EMG and clinical follow-upare required. MA can be differentiated from ALS by symptom onset at younger age in men, its benign course and generally with stabilization of clinical and EMG findings over 2 to 4 years. The differential diagnosis of ALS-like diseases should be done in cases presenting with MA clinic after the age of forty.

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Received by: 09 March 2015
Revised by: 22 May 2015
Accepted: 05 June 2015

The Online Journal of Neurological Sciences (Turkish) 1984-2015
This e-journal is run by Ege University Faculty of Medicine,
Dept. of Neurological Surgery, Bornova, Izmir-35100TR
as part of the Ege Neurological Surgery World Wide Web service.
Comments and feedback:
E-mail: editor@jns.dergisi.org
URL: http://www.jns.dergisi.org
Journal of Neurological Sciences (Turkish)
Abbr: J. Neurol. Sci.[Turk]
ISSNe 1302-1664

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