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Re-evaluation of the symptoms of Hirayama disease through anatomical perspective

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SUMMARY Hirayama disease is a rare disease of the anterior horn motor neuron caused by compression of the cervical spinal cord when the neck is flexed. Cervical myelopathy may accompany the disease. It is characterized by symmetrical or asymmetrical muscle weakness and atrophy of muscles innervated by lower cervical and upper thoracic motor neurons. We recorded two male cases of Hirayama disease between the ages of 15 and 21 based on magnetic resonance imaging (MRI) features obtained from the cervical neutral state and from the flexion position which appeared in the right upper extremity. Loss of strength and atrophy in the right upper extremities was existent in clinical findings of these patients. When MRI was taken in the flexion position, there were dilated veins as hypointense signal void on T2 weighted series in posterior epidural area. The contrast enhancement was seen on these veins. It was observed that the posterior dura was displaced anteriorly and the anterior subarachnoid space was narrow. In cases which show clinical findings such as atrophy and loss of strength, having normal MRI results obtained in the neutral position makes it difficult to diagnose Hirayama Disease. In case of a suspicion of Hirayama disease the diagnosis can be made more easily by MRI taken in the flexion position. These case reports aim to bring Hirayama disease to mind and optimize the management of affected individuals

Keywords cervical myelopathy, Hirayama, Juvenile spinal muscular atrophy, Monomelic amyotrophy, cervical MRI

Hirayama disease was first reported in 1959 in Japan by Keizo Hirayama, *et al.* as "juvenile muscular atrophy of the unilateral upper extremity" (*1*). It also takes place in the literature as "juvenile asymmetric segmental spinal muscular atrophy, benign focal amyotrophy, oblique atrophy due to brachioradial muscle involvement, and monomenic amyotrophy" (*2*).

Although it is seen more often in Asian countries such as Japan, India and Taiwan (*3*) similar cases have been reported from different countries as well. The MRI signal abnormalities and spinal cord atrophy are the characteristic radiological features of the disease. While C5-7 levels are especially affected in patients from western countries, it has been reported in the literature that C7-T1 levels are affected more in patients from Asian countries (*4*).

This disease is seen more often among young men between the ages of 15 and 25, and is characterized by asymmetric muscle weakness and atrophy in related muscles by affecting C7, C8 and T1 myotomes. We diagnosed Hirayama disease after examining the clinical findings and the affected anatomical structures supporting these findigs in the MRI taken in neutral and in flexion position of two male cases, aged 15 and 21, who visited our clinic with the complaint of muscle weakness in the right upper extremities.

1. Clinical manifestation of a rare disease

Case 1 A 15-year-old male patient presented with complaints of progressive weakness in the right forearm and hand for 3 months. The case applied to the clinic in 2021. Patient's anamnesis showed no family history of neuromuscular disease, no comorbidities and no cervical trauma.

clinical evaluation showed that the strength of the right hand interosseal muscles was 3/5, the right thumb abductor muscles, the right wrist and the extensor muscle strength of the 2nd and 5th fingers were evaluated as 4/5 according to Medical Research Council Scale (*5*).

On inspection, atrophy in the first dorsal interosseal muscle of the right hand, and moderate atrophy in the other intrinsic hand muscles and the flexor and extensor muscles of the wrist were observed. The patient did not have loss of sensation and deep tendon reflexes, fasciculation and pain, and tremor was observed only in the fingers. Left upper and lower extremity neurological findings were normal, and there was no sign of pyramidal tract involvement. The signs of Babinski reflex and Hoffman were negative. Laboratory findings were normal.

After the electromyography (EMG) was examined, low amplitude in the activation of the muscles innervated by the right ulnar nerve was discovered while the left ulnar nerve and median nerve activation on both sides were found normal. In summary, active denervation was found on the right side C7, C8 and T1 myotomes. In addition to these clinical findings, MRI examinations were also performed in this patient. Since that the MRI findings in the neutral position were normal, the patient's MRI was taken in the full neck flexion position (by touching mandible to the sternum). As a result of these examinations, posterior internal vertebral plexus (Batson's plexus) dilatation was observed due to the anterior displacement of the posterior dura mater. It was observed that the enlargement in the posterior epidural space disappeared when placed in the neutral position. As a result of these evaluations, the patient was diagnosed with Hirayama disease. The patient and his family were informed of these findings and a conservative treatment was recommended. Since first applied there has been no change in the clinical and neurological findings of the patient.

Case 2 A 21-year-old male patient presented with complaints of weakness in the right upper extremity distal region and hand in 2021. Patient's anamnesis showed no family history of neuromuscular disease, no comorbidities and no cervical trauma. The clinical evaluation showed atrophy in the right thenar region of the right hand, and the muscle strength of the ipsilateral forearm extensor muscles was evaluated as 3/5 according to Medical Research Council Scale (*5*). The patient did not have loss of sensation and deep tendon reflexes, fasciculation or pain. Left upper and lower extremity neurological findings were normal, and there was no sign of pyramidal tract involvement. The signs of Babinski reflex and Hoffman were negative. Laboratory findings were normal.

After EMG was examined, low amplitude in the activation of the muscles innervated by the right median nerve was discovered. In summary, active denervation was found in C5-T1 myotomes. In addition to the clinical findings, MRI examinations were also performed in this patient. In the MRI findings taken in the flexion position, there were dilated veins which contrast enhancement in postcontrast series and which were as hypointense signal void in T2 series in posterior epidural area along the vertebral column begining from the C5 vertebra level to the upper thoracic level. Based on anterior displacement of the posterior wall of the dura mater and narrowing of the subarachnoid space in the anterior, we concluded that this patient had Hirayama disease. The findings described in dynamic MRI were not observed in post-contrast sagittal series taken in neutral position after flexion, and venous engorgement was not detected in this position. Neither a significant atrophy in spinal cord nor signal changes consistent with myelopathy were observed. Since first applied there has been no change in the clinical and neurological findings of the patient.
The informed consent was obtained from the patients for all descriptions (Figure 1 and Figure 2).

2. Insight into Hirayama disease

Theories proposed in the literature for Hirayama disease usually involve the anterior horn of the spinal cord at the lower cervical and upper thoracic levels. Therefore, the disease which has not yet been fully explained is likely to

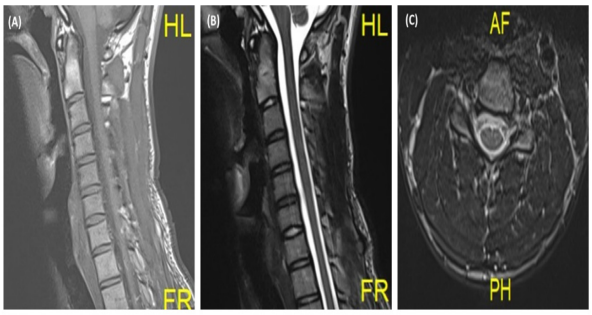

Figure 1. Sagittal turbo spin echo (TSE) T1 (A), sagittal turbo spin echo (TSE) T2 (B), axial turbo spin echo (TSE) T2 (C) images are seen as normal in standard cervical MRI protocol.

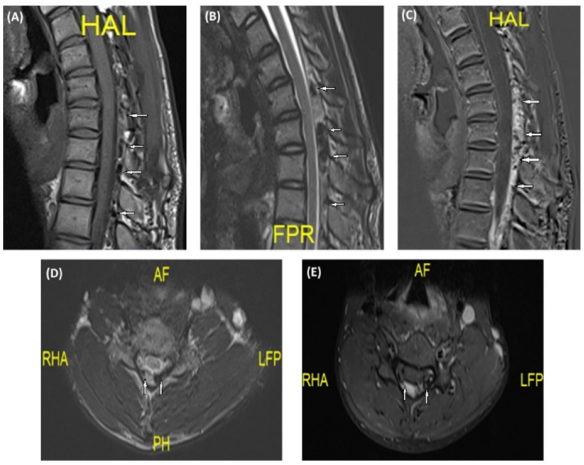

Figure 2. (A) Sagittal turbo spin echo (TSE) T1, sagittal turbo spin echo (TSE) T2 (B), sagittal post-contrast spectral presaturation with inversion recovery (SPIR) (C), axial turbo spin echo (TSE) T2 (D), axial post-contrast spectral presaturation with inversion recovery (SPIR) (E) images are taken in flexion position. In this position, venous engorgement and contrast enhancement (arrows) in posterior epidural space are evident.

be confused with other pathologies and the pathogenesis (*6,7*). The most widely accepted of these theories is cervical myelopathy due to neck flexion, which was introduced by Kikuchi *et al*. (*8*).

Anatomically the spinal dura mater is tightly attached to the dorsal periosteum along the vertebral canal surrounding the spinal nerves in healthy individuals whereas the dura mater in Hirayama patients is loosely attached to the posterior longitudinal ligament within the spinal canal. During cervical flexion, the cervical vertebral column can extend approximately 3 cm and the loose dura mater cannot adapt itself to this significant change in length. According to the theory of Kikuchi *et al*., in patients diagnosed with Hirayama disease, the dura mater remains relatively short and rigid compared to the vertebral canal and cannot compensate for the lengthening of the vertebral canal during neck flexion. During neck flexion, the spinal cord is exposed to compression between the vertebral corpuscles and the dura mater because of the anterior displacement of the posterior dura mater. As a result of repetitive neck flexions, the anterior part of the spinal cord and the vessels feeding the anterior horn (especially the anterior spinal arteries) are exposed to compression resulting in ischemia attacks and ultimately chronic traumas of the anterior horn. In the affected segment, denervation and atrophy occur in related muscles due to the anterior horn compression and the ischemia. The asymmetrical thinning of the lower cervical cord in MRI findings explains this myelopathy in the muscles (*9*) (Figures 3A and 3B).

In both cases where we analyzed the MRI findings, we observed that the posterior wall of the dura mater was displaced anteriorly in the flexion position, causing compression on the spinal cord and venous plexus. However, this pressure disappeared when the neck was put back in the neutral position. In addition, we did not observe significant atrophy of the spinal cord or signal changes consistent with myelopathy on MRI in these two patients. In our cases, as stated in the literature, especially lower cervical region involvement was dominant. The fact that the lower cervical vertebrae (C5-C6-C7) are more involved in the flexion position can explain anatomically the thinning of the spinal cord because of the compression that it was exposed to.

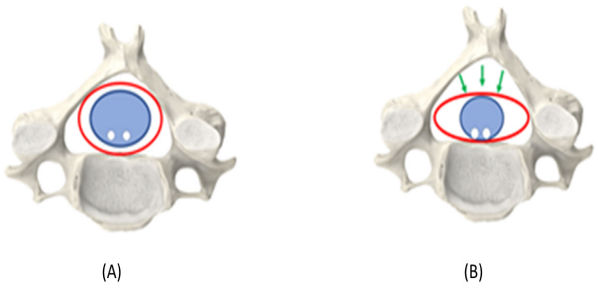

Figure 3. (A) Neutral position of cervical vertebrae. Red line: Spinal dura mater. Blue structure: Cervical spinal cord. The area between red and blue line: Dural sac. White structures: Anterior horn of spinal cord. **(B) Arrows show forward shifting of posterior dura mater on flexion and the compression on the anterior horn Red line: Spinal dura mater.** Blue structure: Cervical spinal cord. The area between red and blue line: Dural sac. White structures: Anterior horn of spinal cord.

There are neuroradiologists and spinal surgeons who claim that the dura mater alone can not be sufficient to explain the mechanism of Hirayama disease because of its rigid structure and its relativelty short stature compared to the bone structure of the vertebral column. Accordingly, it has been suggested that the part of the posterior dural structure adhering to the pedicles is loose even in the neutral position on MRI and the elastic and collagen fibers of the operatively resected dura mater show pathological abnormalities (*7*).

Myodural bridges which have the soft connective tissue connection between the fascia of the suboccipital muscles and the dura are thought to be structures that passively attach the dura mater and act as an active stabilizer for the spinal cord. In other words, these structures are seen as a dural tension monitoring system by restricting the movements of the dura mater (*10*). There are studies in which the etiology of cervicocephalic headache, cervicocephalic pain syndromes and dural pathologies are associated with myodural bridges (*11*). Some neuroanatomists think that the myodural bridges, which they define especially at C1-2 levels, allow anterior displacement of the dura mater in the lower cervical cord; thus cause the Hirayama disease (*7*).

Libin has stated that the cranial bones partially prevent the posterior part of the dura mater from moving forward during neck flexion. Since the dura mater is attached to the base of the cranium, it has been revealed that the sliding movement of the temporal bone, especially by turning backwards on the parietal bone, during cervical flexion prevents the dura mater from making pressure by moving away from the spinal cord (*12*). Therefore, in order not to prevent sliding, the joint type of the temporal bone and parietal bone in this region is squamous rather than sutura (*13*). If this joint were a suture like the other joints in the skull, almost all bones would have to participate in this movement. Based on the above facts, we hypothesize that one of the pathogenesis of Hirayama disease may be the relationship between cranial bone movements and dura mater. We conclude that in addition to the cervical region examination and MRI finding taken during the neck flexion and extension, examining whether there is a problem with the movements of the temporal and parietal bones in these cases as stated above may contribute to the understanding of Hirayama disease (*14*).

In addition to these stated mechanical causes, hyperIgEemia, immunological abnormalities in cytokine and chemokine amounts in serum and cerebrospinal fluid have been reported in patients with Hirayama disease (*7*).

Hirayama disease is likely to be confused with neuromuscular diseases such as spinal muscular atrophy,

amyotrophic lateral sclerosis or structural cervical cord lesions (syringomyoli) due to similar clinical symptoms. Therefore, keeping in mind Hirayama disease can help when conventional examinations result in no diagnosis. In addition to MRI in the neutral position, MRI in neck flexion may be very useful in patients with otherwise normal clinical findings. In MRI results taken in the flexion position in our cases, it was observed that the posterior dura mater was not only displaced anteriorly, but also a band-shaped lesion was formed in the posterior epidural space of the lower cervical canal. This band-shaped structure is related to congestion of the posterior internal vertebral venous plexus rather than vascular venous malformation. The internal vertebral venous plexus is a structure that runs along the entire vertebral canal and is responsible for the venous drainage of the structures therein. This plexus is an alternative route for circulation when the jugular veins are exposed to compression or when there is obstruction of the inferior vena cava. It also acts as a protective cushion and thermoregulation factor for important structures within the vertebral canal (*6*). Because of the fact that the anterior displacement of the dura mater would expose the anterior part of this venous plexus to compression as a result of the compression in Hirayama disease, congestion occurs in the posterior of this plexus. Congestion should not be observed in this anatomical structure in healthy people in the flexion position, but even if this situation in Hirayama patients does not cause a permanent problem in the veins, it is critical for diagnosis as it will cause the appearance of congestion (*15*). In our cases, as stated in the literature, we observed a dilatation in this plexus caused by the dura mater compression on the venous plexus in the flexion position. In MRI, we observed that the vascular structures reverted to their normal anatomical appearance when the neck was placed in neutral position.

There are other useful criteria for the distinctive diagnosis of Hirayama disease. The distinctive features of the disease include muscle weakness and atrophy, especially in distal muscles of upper extremity forearm and hand, unilateral involvement of the upper extremity, and absence of lower extremity involvement. This disease occurs widely among young adult males, progresses in the first few years and remains stable thereafter, having no loss of sensation and abnormal tendon reflexes. In addition, the elimination of other pathologies such as motor neuron diseases, spinal cord tumors, brachial plexopathy, and cervical vertebra abnormalities after examinations should bring Hirayama disease to mind (*16*). In the cases we encountered, loss of strength and atrophy in hand and in the unilateral upper extremity distal region, negative pathological reflexes and the fact that the patients were young adult males suggested Hirayama disease.

Another method of examination to guide the diagnosis process is EMG. There are studies suggesting chronic denervation in the muscles of the same extremity depending on the lesion level in the EMG results of the affected extremity (*1*). In the EMG results of our cases, denervation was observed in the ulnar and median nerve myotomes depending on the level of pressure and lesion.

In addition to the loss of strength, the most common complaint of the patients, irregular tremor was observed in the fingers of the affected upper extremity in the literature (*17*). Our first case where tremor was observed in the patient lends support to this observation.

Right-sided asymmetrical involvement is more common in Hirayama disease and the underlying mechanism of this condition is still unknown. Shinomiya *et al*. explained this with the "posterior epidural ligament factor". Anatomically, the epidural ligaments (Hofmann's ligaments) are connective tissue structures that extend from the dura mater to the vertebral canal. The posterior part of these structures is located between the posterior wall of the dura mater and the ligamentum flavum in the cervical spine. These ligaments prevent the anterior displacement of the dura meter by acting as a tent for it. The 'posterior epidural ligament factor' theory proposes that the posterior wall of the dura mater is displaced anteriorly because of the absence or the unequal distribution from right to left of posterior epidural ligaments and thereby causes an asymmetrical atrophy by creating a pressure in spinal cord. Generally, the more frequent occurrence of Hirayama disease on the right side is attributed to the anatomically abnormal development of the posterior epidural ligaments on this side (*18-21*). Consistent with the literature, the right upper extremities of our cases were also affected.

3. The importance of awareness on Hirayama disease

Hirayama disease is very likely to be overlooked during diagnosis because of similarities in clinical findings with other diseases. Due to the fact that clinical examination and MRI taken in neutral position may be insufficient to support the diagnosis process, it will be useful to further examine the anatomical structures with MRI in flexion position. Therefore, we believe that even if it is seen rarely, awareness of Hirayama disease will lead to correct diagnosis and thus appropriate and early treatment. In addition, this study is unique in that it reveals different anatomical theories about the pathophysiology of Hirayama Disease.

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Conflict of Interest: The authors have no conflicts of interest to disclose.

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