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GRAND ROUNDS

# Hirayama disease

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## Abstract

**Purpose** Hirayama disease is an initially progressive disease caused by cervical neck flexion compressing the anterior horns of the lower cervical spinal cord. It is primarily seen in young males of Indian or Asian descent. With increasing dispersion of these populations this condition is increasingly being encountered internationally. This grand round reviews this rare but increasingly recognized condition.
**Materials and methods** We present a classic case of a young Indian male with progressive hand and forearm weakness. We discuss the typical clinical presentation, appropriate investigations and management of this condition.
**Results** Our patient presented with oblique amyotrophy and underwent a diagnostic flexion MRI scan which revealed anterior translation of the posterior dura with compression of the anterior horns of the lower cervical cord. He has been successfully treated in a cervical collar.
**Conclusions** This case illustrates the typical presentation, diagnostic investigations and treatment of Hirayama syndrome. It is hoped that this review will alert clinicians of this condition and optimize the management of affected individuals.

**Keywords** Hirayama · Oblique amyotrophy · Atrophy · Juvenile spinal muscular atrophy · Juvenile muscular atrophy · Monomelic amyotrophy · Asymmetric segmental spinal muscular atrophy

## Case presentation

Consent was obtained from the patient to use his de-identified clinical data and radiological studies as a published clinical case illustration.

The patient was a 21-year-old male of mixed European–Indian origin who presented to our service with rapid onset and progressive weakening of his left hand grip 1 year

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ago after he started a new job as a manual labourer. He felt this prevented him from lifting heavy objects, and therefore limited his capacity to fulfil his occupational requirements. He also noted intermittent shooting pains into both forearms without sensory deficit and that his symptoms worsened in the cold.

He denied any antecedent injury or significant past medical history and he had no family history of neurological conditions or motor neuron disease.

His clinical examination revealed a healthy looking gentleman, with normal spinal alignment and full neck range of movement (Fig. 1).

He had bilateral oblique amyotrophy with wasting of his forearm and hand musculature but preservation of his brachioradialis, which was worse on his left side (Fig. 2).

He had marked left-sided weakness (MRC 3/5) of wrist and finger flexion and extension as well as the motor function of the small muscles of the hand. On his right side he had subtle (MRC 4/5) power of the same muscle groups. All other motor functions of the limbs and the cranial nerves were normal (MRC 5/5). He had normal reflexes and no myelopathic signs.

Prior to referral he had undergone nerve conduction studies (NCS). These revealed moderate attenuation of the compound motor action potentials (CMAPs) with normal motor conduction velocities. He had normal sensory responses. In addition, his needle electromyography (EMG) showed subacute on chronic neurogenic dysfunction of C8 and T1 to be worse on the left, but otherwise a normal study of all other cervical myotomes. This suggested a bilateral pre-ganglionic dysfunction of C8 and T1 to be worse on the left.

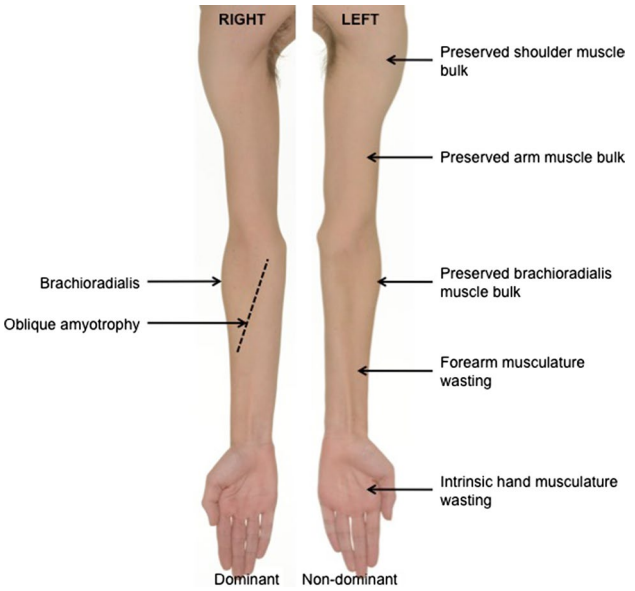


**Fig. 2** Frontal photograph of both upper limbs illustrating the oblique amyotrophy

## Diagnostic imaging

Cervical X-rays showed a loss of normal cervical lordosis in the neutral position, but otherwise no significant abnormalities (Fig. 3).

His flexion and extension views showed a full range of movement, without instability (Fig. 4).

A supine MRI scan in a neutral cervical position revealed no obvious abnormality apart from a loss of cervical lordosis

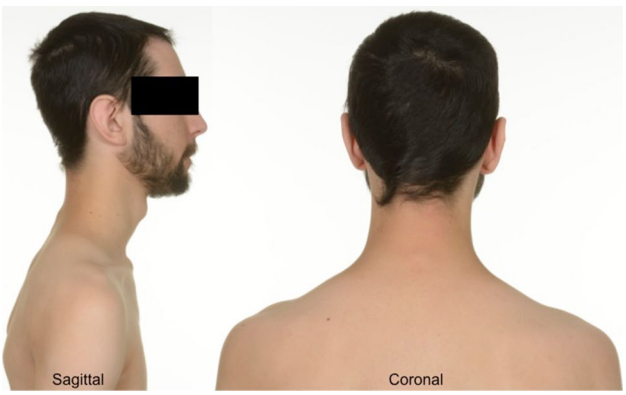


**Fig. 1** Frontal and lateral photographs of the patient's cervical spine in a standing neutral position

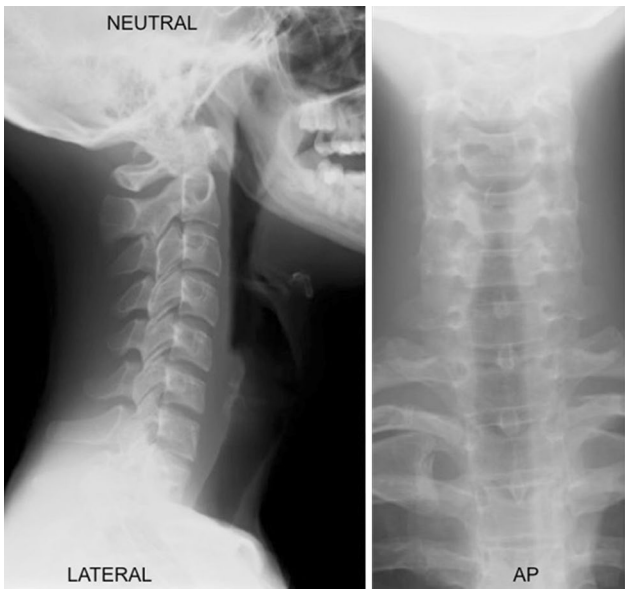


**Fig. 3** Lateral and antero-posterior (AP) standing cervical spine radiographs with the neck in a neutral position

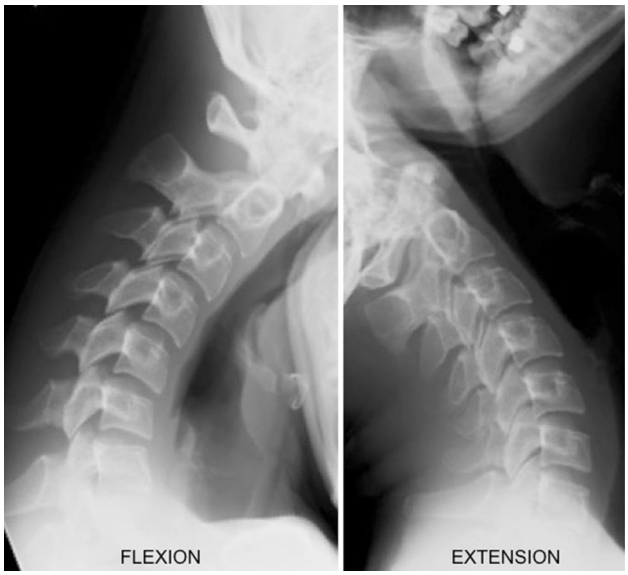


**Fig. 4** Lateral flexion and extension cervical spine radiographs

(Fig. 5a). This was compared to his MRI in cervical flexion, which showed anterior displacement of the posterior dura with detachment from the cervical lamina between C3 and T1 (Fig. 5b). This was associated with a posterior epidural high signal intensity lesion extended from C3 to T1 and a minimally reduced antero-posterior diameter of his lower cervical cord, most notably at the C5/C6 level. An extension MRI confirmed the loss of cervical lordosis and reduction of the posterior dura onto the lamina (Fig. 5c).

## Historical review

Hirayama disease, also previously known as non-progressive juvenile spinal muscular atrophy, juvenile muscular atrophy of the distal upper extremity, monomelic amyotrophy and juvenile asymmetric segmental spinal muscular atrophy, was first described by Keizo Hirayama in 1959 in 12 cases of juvenile muscular atrophy of unilateral upper extremity [1, 2]. Since then the same author described a further 20 patients in 1963 and 38 cases in 1972, cementing the name Hirayama disease [3]. Subsequently, it has primarily been reported in the Asian and Indian literature. However, reports from outside of these geographic regions are increasing, primarily in Europe and North America.

## Epidemiology

This condition is rare, with less than a thousand reported cases. It primarily affects young males (M:F 20:1) aged in their teens or twenties [4]. There is no clear familial relationship with only six pairs reported in over 300 cases [4]. However, there is a higher prevalence in those of Asian and Indian origins [5].

## Diagnosis

### Symptoms

The condition presents as an insidious onset, initially progressive, muscular weakness of the distal upper limbs,

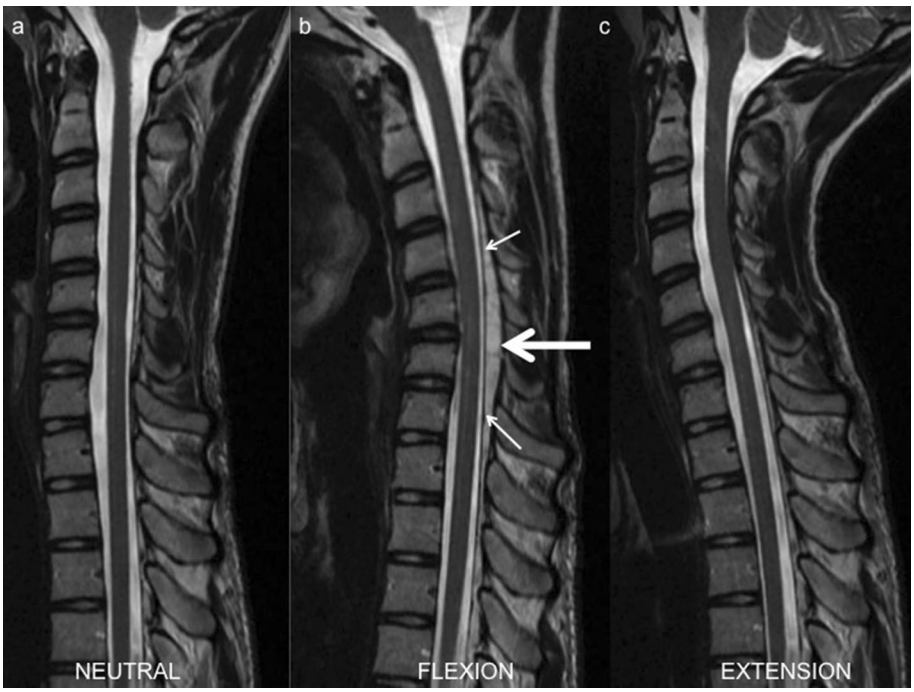


**Fig. 5** Representative mid-sagittal T2 MRI scans in neutral (**a**), flexion (**b**) and extension (**c**). Note the anterior displacement of the posterior dura with de-lamination from the lamina (small arrows) and the defect filled with a high signal intensity lesion (large arrow) in flexion, which reduces in neutral and extension. In addition, note the anterior compression of the cord in the region of C5/6 with neck flexion

particularly affecting the strength of the wrist and fingers with preservation of brachioradialis [4]. The symptoms are most commonly unilateral, occasionally bilateral, but asymmetric, and rarely symmetrically bilateral. Over 95% of patients feel that their weakness worsens in cold environments, termed cold paraparesis [4].

### Signs

The clinical signs include initial progressive muscular wasting and weakness of the hands and forearms, with preservation of brachioradialis, giving the characteristic oblique border of muscular atrophy on both the volar and dorsal forearms, described as oblique amyotrophy [3].

Often, fasciculations are identified when the affected muscles contract, termed contraction fasciculations. However, muscle stretch reflexes are normal and there are no pyramidal signs, urinary disturbances or cranial nerve abnormalities. Sensory function is usually preserved although a few patients describe diffuse hypoesthesia in the hand.

### Investigations

The diagnosis of Hirayama disease is based on clinical suspicion correlated with an MRI in full cervical flexion [6].

Routine supine MRI cervical scans often appear normal and therefore a flexion MRI is mandatory. However, the subtle findings on a routine supine MRI scan with the neck in a neutral position are mild to moderate atrophy of the lower cervical cord [6]. The cord atrophy is often asymmetrical and the more affected side corresponds to the more atrophied limb [6].

The flexion MRI shows anterior shift of the dural sac with the posterior dura displacing anteriorly away from the lamina [6]. This anterior shift results in a reduced antero-posterior dural canal diameter with antero-posterior cord flattening and stretching of the cord around the posterior vertebral bodies and inter-vertebral discs (IVD) [6, 7]. Furthermore, the anterior displacement of the posterior dura creates the classic crescent-shaped lesion with high signal intensity on T1 and T2 images in the posterior epidural space, thought to represent dilation and congestion of the posterior internal vertebral venous plexus [1, 7]. Most authors believe the lesion develops because of the increased posterior epidural space afforded by the anterior displacement of the posterior dura, but others suggest that it is caused by abnormal drainage or an epidural vascular malformation.

Irrespective of the cause, it is imperative to attain full neck flexion, because incomplete neck flexion may fail to reveal these classic findings [6].

In patients unable to tolerate an MRI, a CT myelogram with the neck in the neutral position reveals mild to moderate atrophy of the lower cervical cord in 88% of patients [6]. Furthermore, anterior displacement of the spinal cord with antero-posterior flattening of the cord in neck flexion is seen in 88% of patients with myelography and 94% of patients with CT myelography [6].

Nerve conduction studies, muscle biopsy and cerebrospinal fluid (CSF) analysis are not required to make the diagnosis, but may be used to exclude other conditions.

The electromyography results in Hirayama syndrome show denervation of atrophied muscles and in over 90% of patients also show contra-lateral denervation of the same muscles [4]. Interestingly, despite no evidence of muscle wasting, half of all patients will have evidence of denervation in triceps brachii and less than quarter of patients in biceps brachii, deltoid and brachioradialis [8].

The motor nerve conduction velocities are normal, except occasional minimal slowing in the ulna nerve [9]. The CMAPs have reduced amplitudes in the atrophied muscles [9]. In those with cold paraparesis, cold environments result in decreased amplitudes of CMAPs after high frequency repetitive nerve stimulation [10].

The F waves show mild increased latency, low persistence and singular, high-amplitude waveforms consistent with denervation/reinnervation [9]. The F wave persistency typically decreases with neck flexion during the progressive phase [9].

During spinal cord analysis, the somatosensory evoked potentials (SSEPs) occasionally show abnormal spinal cord conduction [11]. The motor evoked potentials (MEPs) show increased latency and reduced amplitude temporarily aggravated by neck flexion [12].

Muscle biopsies of affected musculature reveal atrophic changes and evidence of reinnervation with clusters of small angular fibres and large type groupings [13].

CSF biochemical analysis is usually normal, but may show a mild increase in the protein content (40–60 mg/dl; normal < 40 mg/dl) [26]. If performed, the Queckenstedt test will likely show a mildly slowed and insufficient rise and fall in the neutral neck position, which worsens with neck flexion [14].

## Pathology

In this condition, it is believed that an imbalance occurs between the growth of the vertebral column and that of the spinal canal contents [1]. Unlike the normal situation, where the spinal dura is slack and loosely anchored cranially to the foramen magnum and posterior surfaces of C2 and C3 and caudally to the coccyx, this mismatch, with the vertebral column longer than the dural sac, results in the spinal cord and meninges being tight and in cervical flexion, and thus stretched around the posterior vertebral bodies [1, 3, 7]. This bowstringing effect is believed to cause focal ischaemia of the anterior horn cells of the lower cervical spinal

cord presumably due to compression of the anterior cord and anterior spinal artery on the posterior vertebra during neck flexion [15, 16]. This results in the insidious onset of amyotrophy, which clinically manifests as weakness with wasting of the forearms and hands, with preservation of brachioradialis (oblique amyotrophy involving C7-T1 myotomes) without sensory or pyramidal signs [4].

The difference in growth rates between males and females has been proposed as the cause of male predominance and the juvenile growth spurt explains the adolescent predominance.

Although it seems likely that a mechanical compression of the anterior spinal artery and anterior spinal cord is the cause of this non-progressive juvenile spinal muscular atrophy, the exact cause of Hirayama disease remains unknown. Particularly, why the condition is also associated with atopy and raised levels of immunoglobulin-E (IgE) [17]. Some authors have suggested that blood stagnates in the region of the compressed cord and subsequently allows platelets to aggregate and release histamine, causing arterial spasm and microcirculatory damage [17]. In support of this hypothesis is the fact that atopy tends to affect younger people, men more than women and Asians more than non-Asians. However, why patients with anterior cord compression from cervical disc protrusions, ossification of the longitudinal ligament (OPLL) and osteophytes tend to develop myelopathy rather than the specific upper limb weakness of Hirayama—despite the mechanical anterior compression being similar—remains unclear.

The hypothesis that there is increased pressure exerted on the lower cervical cord is supported by the MRI findings and the pressure curve of the Queckenstedt test showing a slightly slowed and insufficient rise and fall in the neutral neck position, which worsens with neck flexion [14]. The subsequent microcirculatory disruption primarily affects the anterior horn, which is the most vulnerable structure to ischaemia in the spinal cord.

The effect on the extremity musculature has been confirmed by electromyography which, in single fibre analysis, has revealed an increased fibre density and jitter during the initial progressive phase of the disease with continued increased fibre density, but reduced jitter in the later non-progressive phase consistent with maturation of reinnervation. This reinnervation has been confirmed with forearm muscle biopsies revealing atrophic changes with clusters of small angular fibres and large type groupings consistent with reinnervation [13].

As this is a non-fatal condition affecting young patients, only a few autopsy results are available in older patients who subsequently died of other conditions [15, 16]. However, the macroscopic appearance reveals antero-posterior flattening of the lower cervical cord [15]. The microscopic analysis of the lower cervical cord reveals a reduced antero-posterior diameter of the anterior horns with decreased neuron numbers, mild gliosis and central necrosis without cavity formation [15, 16]. Surviving neurons show varying stages of degeneration. The white matter, posterior horns and vasculature remain normal.

### Differential diagnosis

The main differential diagnosis is motor neuron disease and spinal muscular atrophy. It is differentiated from these conditions by its specific oblique amyotrophy with a non-progressive course and flexion MRI findings, as well as evidence of chronic microcirculatory changes in the anterior spinal artery territory supplying the anterior horn cells of the lower cervical cord [3].

Another differential is a spinal cord infarct, although this typically has a sudden onset and causes significant pain as well as long tract signs in the case of an anterior spinal artery infarct with myelopathy, paralysis, loss of bowel or bladder control and loss of pain and temperature sensation below the lesion, with preservation of the posterior column function including vibration and proprioception sense. Importantly, Hirayama disease does not result from obstruction to the large vessels, but rather affects the intramedullary microcirculation [18].

A more rare condition, tephromalacie anterieur, caused by multiple vascular infarcts resulting in pathological softening of the anterior horns of the lower cervical cord, should also be considered in the differential diagnosis. This condition was described by Marie and Foix in 1912, and is a distal upper limb muscle wasting condition, which affects middle aged or elderly patients. The age and lack of evidence of a dynamic effect on the lower cervical cord during neck flexion differentiates this condition from Hirayama disease.

## Rationale for treatment

Because neck flexion belies the underlying cause of neural disruption in Hirayama disease, it seems logical to prevent this motion in those affected. A cervical collar to prevent neck flexion is a cheap and low morbidity intervention that can be used to prevent neck flexion. Its use in this condition has been studied and has shown excellent results with successful arrest of disease progression in all patients and occasional reversal of symptoms [5, 19].

Operative intervention to prevent cervical flexion has been performed with variable success. However, this approach carries peri-operative risks and long-term sequelae, which need to be considered in an otherwise self-limiting condition.

The benefit of anti-coagulant, anti-histamine or neuromodulator medications has not been evaluated.

## Intervention

Our patient was initially not treated with a cervical collar, but felt that his weakness progressed in his left hand. He was therefore subsequently treated with a soft collar to prevent neck flexion. He has not been treated with anti-coagulants, anti-histamines or neuromodulator medications. He has shown no further progression of neurological dysfunction.

## Outcome

The disease is most commonly self-limiting with spontaneous arrest after initial progression of up to 6 years [4]. The forward displacement of the dural sac and tightening of the spinal cord seen on the flexion MRI reduces with time and corresponds to the clinical course of the disease [4]. Over 60% of patients will show spontaneous arrest of progression within 3 years and 85% within 5 years of diagnosis [4]. With a cervical collar to prevent neck flexion, most will cease progression and some may improve muscular strength and resolution of cold paraparesis [19].

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### Compliance with ethical standards

**Conflict of interest** None of the authors have any potential conflict of interest.

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