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HIRAYAMA DISEASE IN A PATIENT WITH LOEYS-DIETZ SYNDROME: THE FIRST REPORTED ASSOCIATION

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ABSTRACT

Introduction: Hirayama disease (HD) is a rare, self-limiting cervical flexion myelopathy causing progressive, painless distal upper-limb weakness, typically in young Asian males. Loeys-Dietz syndrome (LDS) is a heritable connective tissue disorder due to TGF-β pathway variants, associated with dural ectasia. Their co-occurrence has not previously been reported.

Case description: We describe a 23-year-old woman with genetically confirmed LDS type 2 who developed progressive, painless distal upper-limb weakness, initially unilateral and later bilateral. Examination and electrophysiology showed a C7–T1 polyradicular pattern. Dynamic flexion cervical magnetic resonance imaging (MRI) demonstrated anterior displacement of the posterior dural sac at C5–C7, fully reversible on extension, confirming HD.

Conclusion: This presentation was atypical for HD (female sex, third-decade onset, bilateral course), yet electrophysiological and dynamic-MRI findings were unequivocal. HD should be considered in patients with heritable connective tissue disease presenting with progressive distal upper-limb weakness, irrespective of sex or age, and dynamic flexion MRI is essential for diagnosis.

KEYWORDS

Hirayama disease, Loeys-Dietz syndrome, cervical flexion myelopathy, dural ectasia, connective tissue disorder

LEARNING POINTS

- Hirayama disease should be considered in progressive, painless distal upper-limb weakness even outside its classic demographic (young Asian males), including in women and in patients with an underlying connective tissue disorder.
- Dynamic (flexion) cervical magnetic resonance imaging is required to demonstrate the anterior dural sac displacement that confirms the diagnosis and avoids unnecessary immunomodulatory treatment.
- Heritable connective tissue disorders such as Loeys-Dietz syndrome may modify cervical dural biomechanics, and internists should be aware of neuromuscular complications beyond the classical cardiovascular, skeletal and dural manifestations.

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INTRODUCTION

Hirayama disease (HD) is a rare, self-limiting cervical flexion myelopathy first described in 1959. It presents with slow-evolving, painless, progressive distal upper-limb weakness in a C7–T1 distribution, predominantly in young Asian males (male-to-female ratio ~20:1), caused by anterior displacement of the posterior dural sac during neck flexion and consequent microcirculatory injury to the lower cervical anterior horn cells[1]. Loeys-Dietz syndrome (LDS) is a rare autosomal dominant connective tissue disorder due to pathogenic variants in TGF-β signalling genes *(TGFBR1, TGFBR2, SMAD2, SMAD3, TGFB2* and *TGFB3)*, characterised by aortic and systemic arterial disease, craniofacial anomalies, skeletal dysraphism, and dural ectasia[2]. We report the first case of HD occurring in a patient with genetically confirmed LDS type 2.

CASE DESCRIPTION

A 23-year-old woman with genetically confirmed LDS type 2 (TGFBR2 c.1381T>C; p.Cys461Arg, heterozygous), with a history of surgically corrected triple-curvature scoliosis (age 15), craniosynostosis (surgically managed at age 9), sacral dural ectasia with radicular cysts, aortic root dilatation (sinuses of Valsalva 32.5 mm, Z-score 2.9), and a coiled right terminal internal carotid artery aneurysm (3 mm), was referred to our clinic for a one-year history of progressive, painless weakness of the right hand. Over the year prior to evaluation, she developed involuntary flexion posturing of the 4th–5th digits of the right hand, followed by progressive weakness of more proximal muscle groups; in the months before evaluation, analogous posturing emerged in the left hand. General examination revealed a bifid uvula, bilateral arachnodactyly *(Fig.1)*, and arm-to-trunk disproportion, with a papyraceous scar consistent with prior scoliosis surgery, left dorsal scoliosis, and markedly reduced trunk flexion. She also had facial milia, pectus excavatum, micrognathia and dental crowding. Neurological examination showed bilateral exotropia and diffuse bilateral upper-limb hypotrophy *(Fig. 1)* with periscapular wasting and left scapular winging. The pattern of upper-limb weakness is detailed in *Table 1*. Sensation and stretch reflexes were normal in all four limbs, and lower-limb strength was entirely normal.

Nerve conduction studies (NCS) of the right upper limb showed normal sensory responses in the median, ulnar and radial nerves, and normal motor conduction velocities without conduction block. Notably, the compound muscle action potential (CMAP) amplitude of the right abductor pollicis brevis (APB, 4.2 mV) was markedly reduced relative to the abductor digiti minimi (ADM, 12.0 mV), despite both values remaining within the normal range and with entirely intact sensory conduction.

Needle electromyography demonstrated chronic neurogenic changes (increased motor unit potential amplitude, reduced recruitment) restricted to C8–T1 myotomes. Brachial plexus magnetic resonance imaging (MRI) showed subtle signal alteration in the right C6–C7 postganglionic trunks without gadolinium enhancement, interpreted as positional rather than inflammatory. Cervical spine MRI in neutral position demonstrated loss of cervical lordosis, subtle cord atrophy at C5–C7, and loss of posterior dural attachment. Dynamic flexion (MRI) confirmed anterior displacement of the posterior dural sac at C5–C7 with widening of the posterior epidural space and homogeneous enhancement of the epidural venous plexus, fully reversible on extension *(Fig. 2)*. These changes are pathognomonic of HD[3].

Given the initial diagnostic uncertainty in the context of LDS — which independently raised concern for vascular myelopathy, inflammatory plexopathy, and multifocal motor neuropathy — an empirical course of intravenous immunoglobulin was administered without benefit before



Figure 1. *Clinical photograph of the arms showing arachnodactyly and forearm muscle wasting.*

Muscle	Right (MRC)	Left (MRC)
Deltoid	5	5
Triceps brachii	5	5
Biceps brachii	5	5
Wrist extension	4	5
Pronator teres	3	5
Pronator quadratus	3	5
Extensor digitorum communis	4	5
Flexor carpi radialis	3	4
FDP 2-3	4	5
Flexor pollicis longus	4	5
Lumbricals	4–	5
Abductor pollicis brevis	0	4
First dorsal interosseous	4–	5

Table 1. *Manual muscle testing (MRC scale) in selected upper-limb muscles. The distribution reflects a C7–T1 preferential pattern in the right arm.*

Abbreviations: FDP, flexor digitorum profundus; MRC, Medical Research Council.

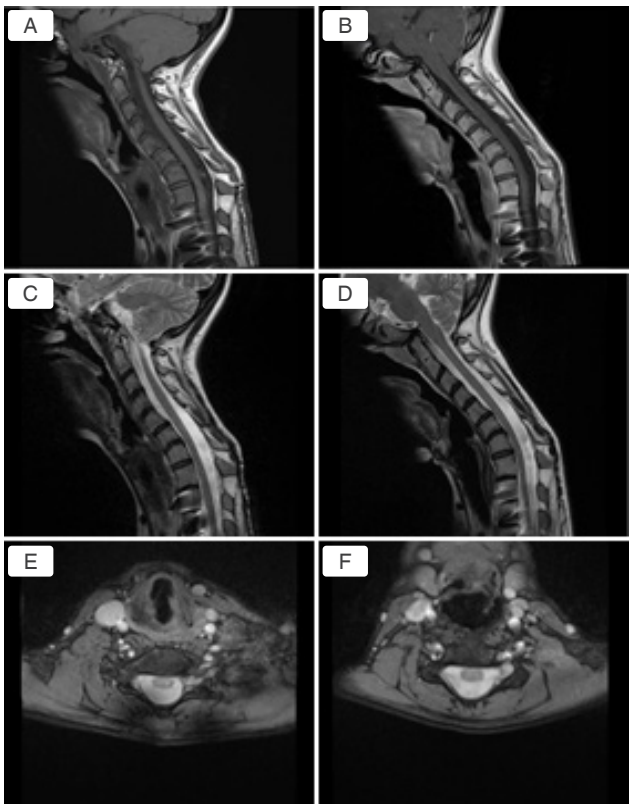


Figure 2. *Cervical spine magnetic resonance imaging in a woman with Loeys-Dietz syndrome type 2 and Hirayama disease.*

Panels in neutral position: A) T1-weighted and C) T2-weighted sagittal images showing loss of normal cervical lordosis, localised cord atrophy at C5–C7, and loss of posterior dural attachment to adjacent laminae.

Panels in full neck flexion: B, D) Anterior displacement of the posterior dural sac at C5–C7, widening of the crescent-shaped posterior epidural space with homogeneous gadolinium enhancement consistent with epidural venous plexus engorgement, and anterior contact of the thecal sac with the posterior vertebral bodies. Changes fully resolved on return to neutral position. These dynamic findings are pathognomonic of Hirayama disease.

Axial panels: E) T2-weighted axial images at the level of C5 and F) C7 showing displacement of the dural sac and asymmetric cord flattening, with anterior horn hyperintensity at C7.

dynamic MRI established the diagnosis. The patient was subsequently fitted with a cervical collar to prevent neck flexion and referred to neurosurgery for evaluation of surgical management.

DISCUSSION

The diagnosis in this case underscores the importance of careful clinical semiology. The pattern of weakness was consistent with a C7–T1 polyarticular distribution rather than a plexopathic or multiple mononeuropathic distribution. Neurogenic preganglionic electrophysiological features and pathognomonic dynamic flexion MRI findings supported the diagnosis of HD[3,4].

Three features render this presentation atypical for HD: female sex, onset in the third decade, and an initially unilateral but rapidly bilateralising course. None of these, however, is incompatible with the diagnosis. Cases of women with HD, although uncommon, are well documented, particularly outside East Asia[5]; bilateral, including bilaterally symmetric, presentations have also been reported[6]; and onset beyond the classic adolescent window is increasingly recognised as the geographic and phenotypic spectrum of HD widens. Critically, the diagnosis here did not rest on demographic pattern-matching but on convergent electrophysiological and pathognomonic dynamic-MRI findings, which remain the diagnostic gold standard irrespective of the patient's age, sex or laterality[3].

The association between HD and connective tissue abnormalities is not without precedent. Generalised joint hypermobility has been identified in approximately 24% of HD patients and correlates with greater cervical range of motion and more severe motor unit loss[7]. Hommel et al. reported juvenile muscular atrophy of the distal upper extremities in a male patient carrying a pathogenic FLNA mutation conferring X-linked periventricular heterotopia with Ehlers-Danlos-like features, highlighting that connective tissue dysregulation may contribute to cervical dural biomechanical vulnerability[8]. More recently, HD has been described in a European patient with an unspecified hypermobility syndrome[9]. To the best of our knowledge, the present case is the first description of HD in a patient with LDS.

LDS raises an intriguing mechanistic question. Classical HD pathophysiology invokes a mismatch between a relatively short dural sac and a longer vertebral column during the adolescent growth spurt[3]. LDS, by contrast, is characterised by connective tissue laxity and dural ectasia — previously documented at the sacral level in our patient[10]. Whether TGF-β-mediated extracellular matrix remodelling modifies cervical dural compliance in a way relevant to HD susceptibility, or whether the extensive skeletal deformity and prior thoracolumbar instrumentation altered spinal biomechanical loading, cannot be determined from a single case. We refrain from a causal claim but consider the association worthy of future attention.

For the practising internist, this case reinforces that the neuromuscular complications of heritable connective tissue disorders extend beyond the well-recognised cardiovascular, skeletal and dural manifestations. Progressive, painless distal upper-limb weakness in such patients should prompt dynamic, position-dependent neuroimaging rather than reflexive immunomodulatory therapy.

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