Neurological Sciences (2019) 40:1743–1747
https://doi.org/10.1007/s10072-019-03758-x

LETTER TO THE EDITOR

# Is Hirayama a Gq1b disease?

Sezin Alpaydın Baslo[1] · Mücahid Erdoğan[1] · Zeynep Ezgi Balçık[1] · Oya Öztürk[1] · Dilek Ataklı[1]

Received: 13 November 2018 / Accepted: 7 February 2019 / Published online: 23 February 2019


## Introduction

Hirayama disease (HD) or juvenile muscular atrophy of distal upper extremity is a rare benign disease of motor neurons that commonly affects the cervical spinal segments. It is more prevalent in males and mostly seen in teens and early 20s. Slowly progressive unilateral or asymmetrically bilateral weakness of hands and forearms is typical. Sensory disturbances, autonomic and upper motor neuron signs are extremely rare [1]. As the synonym "benign focal amyotrophy" implies, it reaches a plateau after a few years. Electromyography reveals asymmetrical chronic denervation in C7, C8, and T1 myotomes. Preservation of C6 myotomes is remarkable. Supportive MRI findings are anterior shift of posterior dura, enlargement of epidural space, and venous congestion under neck flexion.

Recently, serum anti-ganglioside antibodies and their association with motor neuron diseases have become a conflict of interest. Elevated levels of anti-ganglioside antibodies in motor neuron diseases had been reported with different rates ranging between 5 and 57% [2, 3]. However, so far to our knowledge, the association between HD and anti-ganglioside antibodies has not been reported before.

We herein, present a young male patient who got the diagnosis of HD, with unilateral complains but bilateral asymmetrical hand muscle weakness and atrophy accompanied by bilateral electrophysiology and typical MRI findings. His serum was strongly positive (138%) for anti-GQ1b IgG antibody that is worth to be mentioned as a notable bystander.

Informed consent was obtained from the patient included in the study.

## Case

A 17-year-old male was admitted with a 1 year's history of slowly progressive weakness and atrophy of right hand and forearm. He also mentioned the tremulousness of both hands for 6 months. He had no past medical history, and his family history was not significant. Neurological examination revealed atrophy of his right hand intrinsic (Fig. 1) and forearm muscles with preservation of brachioradialis. He had weakness of both-sided digit abduction, adduction, and thumb opposition, with predominance on the right. Palmar grasps were also impaired. No upper motor neuron signs were observed. Sensorial examination was normal. No autonomic signs were noted. Complete blood count and biochemistry were normal. Viral serology, markers for vasculitis, and malignancies were negative.

Nerve conduction studies (NCS) revealed reduced ulnar nerve compound muscle action potential (CMAP) amplitudes bilaterally which was more prominent at the symptomatic side. Median nerve CMAP amplitudes were in between normal ranges bilaterally although slightly lower in the symptomatic right side compared to the asymptomatic left side (Fig. 2). No conduction block was observed throughout the nerve course. The ulnar/median CMAP ratio was 0.34 (2.7/7.9 mV) on the right side and 0.43 (5.2/12.1 mV) on the left. Sensory NCS were normal. Electromyography (EMG) revealed motor unit potentials with increased amplitude, prolonged duration, and a reduced interference pattern at

✉ Sezin Alpaydın Baslo
sznalpaydin@gmail.com

Mücahid Erdoğan
erdoganmucahid@gmail.com

Zeynep Ezgi Balçık
zeynepezgi33@hotmail.com

Oya Öztürk
oyaztrk@yahoo.com

Dilek Ataklı
dilakatakli@gmail.com

[1] Department of Neurology, University of Health Sciences, Bakirkoy Prof. Dr. Mazhar Osman Training and Research Hospital for Psychiatric, Neurologic, and Neurosurgical Diseases, Zuhuratbaba mah. Dr. Tevfik Sağlam cad. No: 25/2 Posta Kodu: 34147 Bakırköy, Istanbul, Turkey

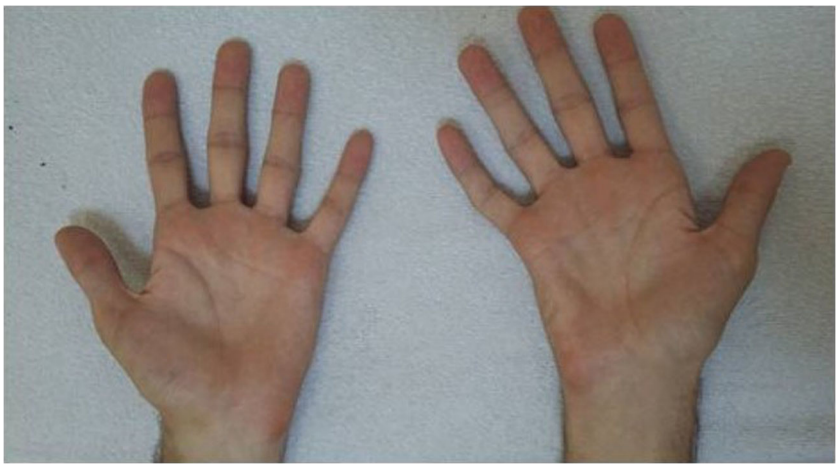

**Fig. 1** Wasting of intrinsic hand muscles, note the right side prominence

maximal effort in muscles of bilateral C7, C8, and T1 myotomes. Mild ongoing denervation activity was also observed distally at right side. F waves were unelicitable in response to right ulnar and left median nerve stimulation. Although the persistence of F waves recorded with left-sided ulnar nerve stimulation was full, the amplitudes were increased.

The MRI at neutral position revealed a slight atrophy of spinal cord at C6 and C7 levels and high signal intensity at C3–C6 levels. Flexion of the neck showed forward displacement of posterior dural sac with engorgement of posterior epidural space. Epidural venous plexus became prominent with flow void signals (Fig. 3). Cranial MRI was not significant. Cerebrospinal fluid direct examination and biochemistry were normal.

The presence of serum antibodies was determined with an enzyme-linked immunosorbent assay (ELISA) (Table 1). Serum anti-GM-1, anti-GM2, anti-GD1a, anti-GD1b IgG and IgM, and anti-GQ1b IgM were negative. However, serum anti-GQ1b IgG was strongly positive (138%) (normal ranges: negative < 30%, greyzone 30–50%, positive 50–100%, strongly positive > 100%).

Overall, clinical features and electrophysiological and radiological findings of our patient were supportive for HD. With the diagnosis of HD, he was referred to rehabilitation clinic. In order to prevent further cord injury, physiotherapy and cervical collar were recommended.

## Discussion

HD was first reported as juvenile muscular atrophy of unilateral upper extremity by Hirayama et al. in 1959 [1]. Synonyms that have been used previously are “juvenile asymmetric segmental spinal muscular atrophy”, “monomelic amyotrophy”, “oblique atrophy” (due to brachioradialis sparing), and “benign focal amyotrophy”. It is a rare and benign disease of motor neurons presented as weakness and wasting of upper extremity muscles unilateral or asymmetrically bilateral.

| Nerve/ Stimulation Site | Recording Site | Latency (ms) | | Amplitude (mV) | | Velocity (m/s) | |
|---|---|---|---|---|---|---|---|
| Median/ | | (R) | (L) | (R) | (L) | (R) | (L) |
| Wrist | APB | 3,8 | 3,6 | 9,6 | 12,1 | | |
| Elbow | | 8,8 | 7,5 | 7,1 | 10,1 | 57 | 67 |
| Axilla | | 11,2 | 11,0 | 7,0 | 10,1 | 60 | 56 |
| Ulnar/ | | (R) | (L) | (R) | (L) | (R) | (L) |
| Wrist | ADM | 3,0 | 2,8 | 2,7 | 5,2 | | |
| Lower elbow | | 7,3 | 6,7 | 2,6 | 5,2 | 59 | 58 |
| Upper elbow | | 9,2 | 8,5 | 2,5 | 5,2 | 51 | 60 |
| Axilla | | 11,4 | 10,8 | 2,5 | 5,2 | 55 | 67 |
| Peroneal/ (R) | | | | | | | |
| Ankle | EDB | 5,3 | | 5,6 | | | |
| Head of fibula | | 13,3 | | 5,3 | | 44 | |
| Posterior knee | | 15,6 | | 5,2 | | 48 | |
| Tibial/ (R) | | | | | | | |
| Ankle | AH | 5,6 | | 11,9 | | | |
| Posterior knee | | 16,5 | | 9,5 | | 42 | |

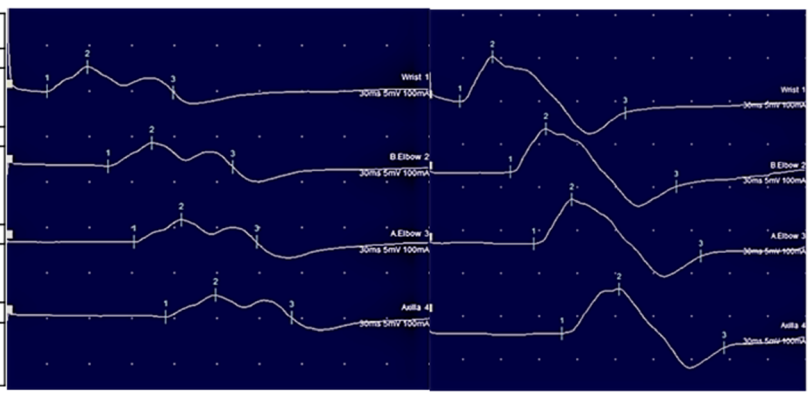

**Fig. 2** Motor nerve conduction studies and CMAPs recorded from right and left m. abductor digiti minimi by ulnar nerve stimulation at wrist, respectively. No conduction block was observed by proximal stimuli [APB Abductor pollicis brevis, ADM abductor digiti minimi, EDB extensor digitorum brevis, AH abductor hallucis, (R) right, (L) left]

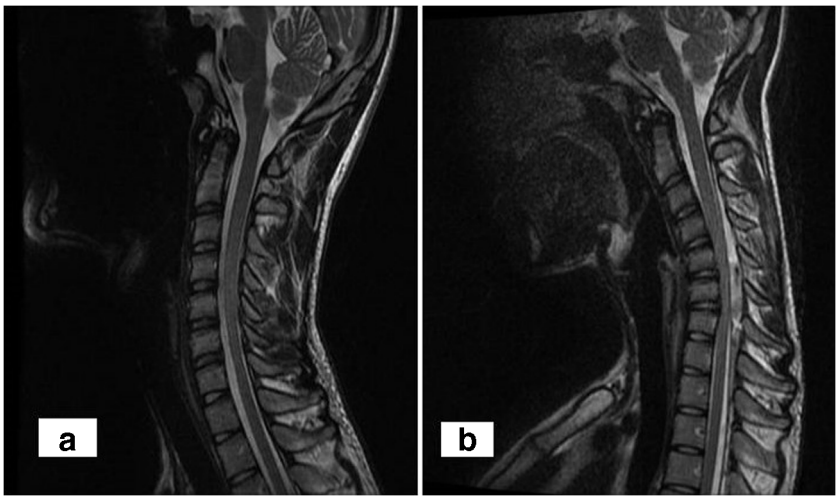


**Fig. 3** T2-weighted MRI of the cervical spinal cord (**a**). Neutral position showed a slight cord atrophy at C6–C7 and high signal intensity at C3-C6 levels (**b**). Anterior shift of posterior dura, engorgement of posterior epidural space, and congestion of epidural venous plexus with neck flexion

Typically, C7, C8, and T1 myotomes are involved and C6 is spared. It is more prevalent in males between the ages of 15 and 25 years. Onset is insidious and slowly progressive, with a plateau seen in a few years [4]. Approximately 80% of the patients complain about worsening of symptoms with cold [5]. Irregular tremors named "minimyocloni" may be seen as well. Cranial neuropathies, sensorial, pyramidal signs, autonomic disturbances, and cerebellar deficits are extremely rare [6].

The disease is described as sporadic but rare familial forms have also been reported [7]. Pathogenesis is still debated. Spinal cord ischemia caused by a mechanical stress (either cervical flexion or disproportional growth of spinal column), or by some autoimmune processes, have been accused. Genetic disturbances were suggested as well. Hirayama et al. pointed the disease onset as approximately 2 years after the longitudinal growth peak in juvenile patients and speculated that HD might be related to a disproportional growth of spinal column and the structures in it [8]. Similarly, "imbalanced growth" hypothesis of Toma proposed compression of spinal cord by inflexible dura during neck flexion and spinal cord atrophy due to repetitive neck flexions and microtraumas [8, 9]. Tashiro et al. stated that male predominance may be explained by faster growth in males than females during puberty which is in parallel to Toma's hypothesis [10]. Khadilkar et al. reported proportionally longer neck comparing to the whole spine which was expressed as low spine to neck ratio in HD patients (mean value of 5.6) than non-HD patients (mean value of 6.15), a factor probably contributing to the dynamic changes with a proof of imbalanced growth [11]. Our patient, a 17-year-old male, was 1.88 m tall and had a whole spine to neck ratio of 4.7 (85:18), which supports the faster and disproportional growth hypothesis of the spinal column. On the other hand, Hirayama et al. also noted macroscopic flattening of the antero-posterior axis of the cervical spinal cord at the C7–8 levels (8), and microscopy revealed anterior horns shorter than half of the anterior-posterior diameter of the spinal cord. This is what "dynamics" hypothesis of Hirayama suggests: circulatory insufficiency and central necrosis in the anterior horns (particularly at C7 and C8 levels) and various degeneration of the large and small neurons at the periphery during neck flexion. Apart from imbalanced growth and dynamics hypothesis, elevated serum IgE levels and atopy were also reported as a precipitator immunologic factor in HD patients [12].

**Table 1** Serum anti-ganglioside antibody panel

| | Result | Value (%) |
|---|---|---|
| Anti-Asialo GM1 IgG | Negative | 5 |
| Anti-Asialo GM1 IgM | Negative | 6 |
| Anti-GM 1 IgG | Negative | 5 |
| Anti-GM1 IgM | Negative | 7 |
| Anti-GM2 IgG | Negative | 5 |
| Anti-GM2 IgM | Negative | 11 |
| Anti-GD1a IgG | Negative | 5 |
| Anti-GD1a IgM | Negative | 4 |
| Anti-GD1b IgG | Negative | 5 |
| Anti-GD1b IgM | Negative | 5 |
| Anti-GQ1b IgG | Strongly positive | 138 |
| Anti-GQ1b IgM | Negative | 4 |

Negative < 30%; greyzone 30–50%; positive 50–100%; strongly positive > 100%

Distal spinal muscular atrophy, amyotrophic lateral sclerosis (ALS), postpolio syndrome, multifocal motor neuropathy with conduction blocks (MMNCB), peripheral neuropathies including anterior interosseous syndrome or ulnar neuropathy, brachial neuritis, thoracic outlet syndrome, syringomyelia, spinal cord tumors, and cervical spondylotic myelopathy (CSM) should be considered in the differential diagnosis of HD. All were excluded in our case via clinical, electrophysiological, and radiological findings [13].

Electrophysiology of HD reveals asymmetrical low CMAPs without conduction block, recorded from the affected myotomal muscles (C7, C8, and T1). Sensorial nerve conduction studies of the same segments should be normal. EMG of the affected muscles shows evidence of chronic denervation but acute denervation potentials may accompany as well. C6 myotome is usually preserved. In our patient, both median and ulnar CMAP amplitudes were lower in the symptomatic right side, and EMG revealed chronic denervation in muscles of C7, C8, and T1 myotomes bilaterally. Mild degree of acute denervation was found in right-sided distal muscles. The ulnar/median CMAP ratio was reported to be lower in HD than healthy subjects, and an ulnar/median CMAP ratio of less than 0.6 was strongly indicative for HD diagnosis [14]. In our patient, the ulnar/median CMAP ratios of both right and left sides were less than 0.6 (0.34 and 0.43, respectively). Repeater F waves with larger amplitudes and increased number of repeater F waves during neck flexion [15] were also reported. Recently, Park et al. reported the reversible prolongation of N13-N20 interpeak latency during neck flexion in a limited number of HD patients suggesting direct compression of lower cervical spinal cord during neck flexion [16].

Dynamic MRI, which is a cervical MRI performed in flexion posture, shows disease-specific findings such as the anterior shift of posterior dura, widening of the posterior epidural space, venous congestion, and contrast enhancement in the posterior epidural space [17]. Chen et al. described that the anterior shift of posterior dura, the most important finding in HD, arose from the disproportionate lengthening of the dura and vertebral column [18]. MRI of our patient revealed anterior shift of posterior dura, engorgement of posterior epidural space, and congestion of epidural venous plexus with neck flexion. In another study, Chen and his colleagues proposed that the clues about HD can also be seen in cervical MRI acquired at neutral position, namely localized cord atrophy, asymmetrical cord flattening, loss of the attachment of dura to adjacent lamina, and increased signal in the non-compressed cord in T2. [19]. Cord atrophy at C6–C7 levels and high signal intensity at C3–C6 levels were other MRI findings that support the HD diagnosis in our patient.

Anti-GQ1b antibodies are anti-ganglioside antibodies associated mostly with Fisher Syndrome (FS), the Guillain-Barré variant characterized by the triad of ataxia, ophthalmoplegia, and areflexia. Sera and purified IgG fraction of FS patients with anti-GQ1b antibodies have been shown to have role in failure of acetylcholine release at neuromuscular junction [20]. The frequency of antibodies against gangliosides reported in ALS patients was in a wide range (0–78%) [3]. Niebroj-Dobosz et al. concluded that elevated antibodies in some ALS patients occurred as manifestation of an autoimmune response to decreased activity, but this was rather an epiphenomenon of neuronal degeneration [21]. Pestronk et al. reported IgM anti-GM1 antibodies were more frequent in ALS patients presenting with prominent lower motor neuron signs [22]. However, no significantly higher levels of other gangliosides antibodies (GQ1b, GD1b, GD1a, GM2, GA1) were reported in ALS patients compared to healthy controls except anti-GM1 which is associated with multifocal motor neuropathy (MMN) [3]. Therefore, we thought, as seen in our patient, elevated anti-ganglioside antibody levels may also be seen in some other forms of motor neuron diseases as a speculative sign of neural injury. Apart from anti-GM1 antibodies, anti-ganglioside antibodies in motor neuron diseases seem to be not suitable to be used as a diagnostic or prognostic marker. These kinds of associations are rare and important to report; however, we thought that the association seen between HD and anti-GQ1b IgG antibody, as reported above, is most probably not reliable, and not proper for a diagnostic or prognostic factor, but may be an indirect sign of anti-ganglioside antibody-mediated nerve injury.

In summary, asymmetrical atrophy and weakness suggests an anterior horn cell lesion unless a pyramidal finding is evident. Absence of sensorial symptoms and findings excludes plexopathies and peripheral neuropathies. Clinical and electrophysiological demonstration of involvement of C7-C8-T1 myotomes by means of “oblique atrophy” in a young male patient with typical MRI findings supports the diagnosis of HD and may save the patient from unnecessary treatments [23]. Anti-ganglioside antibody association as reported with some other forms of motor neuron diseases may substantiate the immune pathogenesis and may speculate an antibody-mediated nerve injury in HD.



## References

1. Hirayama K, Toyokura Y, Tsubaki T (1959) Juvenile muscular atrophy of unilateral upper extremity: a new clinical entity. Psychiatr Neurol Jpn 61:2190–2198
2. Coban A, Ulusoy C, Giris M, Turan S, Turkoglu R, Tuzun E, Idrisoglu HA (2013) Serum anti-neuronal antibodies in amyotrophic lateral sclerosis. Int J Neurosci 123(8):557–562
3. Kollewe K, Wurster U, Sinzenich T, Körner S, Dengler R, Mohannadi V et al (2015) Anti ganglioside antibodies in amyotophic lateral sclerosis revisited. PLoS One 10(4):e0125339
4. Liao MF, Chang HS, Chang KH, Ro LS, Chu CC, Kuo HC, Lyu RK (2016) Correlations of clinical, neuroimaging, and electrophysiological features in Hirayama disease. Medicine 95(28):e4210
5. Zhou B, Chen L, Fan DS, Zhou D (2010) Clinical features of Hirayama disease in mainland China. Amyotroph Lateral Scler 11:133–139
6. Yoo SD, Kim H-S, Yun DH, Kim DH, Chon J, Lee SA, Lee SY, Han YJ (2015) Monomelic amyotrophy with upper motor neuron signs: a case report. Ann Rehabil Med 39(1):122–127
7. Andreadou E, Christodoulou K, Manta P, Karandreas N, Loukaidis P, Sfagos C, Vassilopoulos D (2009) Familial asymmetric distal

upper limb amyotrophy (Hirayama disease): report of a Greek family. Neurologist 15:156–160
8. Hirayama K (2000) Juvenile muscular atrophy of distal upper extremity (Hirayam adisease). Intern Med 39:283–290
9. Toma S, Shiozawa Z (1995) Amyotrophic cervical myelopathy in adolescence. J Neurol Neurosurg Psychiatry 58:56–64
10. Tashiro K, Kikuchi S, Itoyama Y, Tokumaru Y, Sobue G, Mukai E, Akiguchi I, Nakashima K, Kira JI, Hirayama K (2006) Nation wide survey of juvenile muscular atrophy of distal upper extremity (Hirayama disease) in Japan. Amyotroph Lateral Scler Other Motor Neuron Disord 7:38–45
11. Khadilkar S, Patel B, Bhutada A, Chaudhari C (2015) Do longer necks predispose to Hirayama disease? A comparison with mimicks and controls. J Neurol Sci 359:213–216
12. Anuradha S, Fanai V (2016) Hirayama disease: a rare disease with unusual features. Case Rep Neurol Med 2016:5839761
13. Bademkiran F, Oto A, Tabakoglu A, Aydogdu İ, Uludag B (2015) Monomelik amyotrophy (Hirayama disease): clinical findings, EMG characteristics and differential diagnosis. JNS (Turkish) 45: 558–565
14. Jin X, Jiang J, Lu F, Xia X, Wang L, Zheng C (2014) Electrophysiological differences between Hirayama disease, amyotrophic lateral sclerosis and cervical spondylotic amyotrophy. BMC Musculoskelet Disord 15:349
15. Zheng C, Zhu Y, Yang S, Lu F, Jin X, Jiang J (2016) A study of dynamic F-waves in juvenile spinal muscular atrophy of the distal upper extremity (Hirayama disease). J Neurol Sci 367:298–304
16. Park JS, Ko JY, Park D (2019) The reversible effect of neck flexion on somatosensory evoked potentials in patients with Hirayama disease: a preliminary study. Neurol Sci 40:181–186
17. Yuksel M, Kalemci O, Yüksel KZ, Erguden C, Yucesoy K (2009) Hirayama hastalığı ve tanıda manyetik rezonans görüntülemenin önemi. Sinir Sistemi Cerrahi Derg 2:191–195
18. Chen CJ, Chen CM, Wu CL, Ro LS, Chen ST, Lee TH (1998) Hirayama disease: MR diagnosis. AJNR 19:365–368
19. Chen CJ, Hsu HL, Tseng YC, Lyu RK, Chen CM, Huang YC, Wang LJ, Wong YC, See LC (2004) Hirayama flexion myelopathy: neutral-position MR imaging findings— importance of loss of attachment. Radiology 231:39–44
20. Uncini A, Lugaresi A (1999) Fisher syndrome with tetraparesis and antibody to GQ1b: evidence for motor nerve terminal block. Muscle Nerve 22:640–644
21. Niebroj-Dobosz I, Jamrozik Z, Janik P et al (1999) Anti-neural antibodies in serum and cerebrospinal fluid of amyotrophic lateral sclerosis (ALS) patients. Acta Neurol Scand 1999 100:238–243
22. Pestronk A, Adams RN, Clawson L et al (1988) Serum antibodies to GM1 ganglioside in amyorophic lateral sclerosis. Neurology 28: 1457–1462
23. Rosliakova A, Zakroyshchikova I, Bakulin I, Konovalov R, Kremneva E, Krotenkova M, Suponeva N, Zakharova M (2019) Hirayama disease: analysis of cases in Russia. Neurol Sci 40:105–112