Clinical Neurophysiology 131 (2020) 1311–1319

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Establishment of a clinician-led guideline on the diagnosis and treatment of Hirayama disease using a modified Delphi technique

Feizhou Lyu [a,b,1], Chaojun Zheng [a,1], Hongli Wang [a], Cong Nie [a], Xiaosheng Ma [a], Xinlei Xia [a], Wei Zhu [a], Xiang Jin [a], Yongcheng Hu [c,2], Yu Sun [d,2], Yu Zhu [e], Satoshi Kuwabara [f], Rosa Cortese [g], Kaukab Maqbool Hassan [h], Keisuke Takai [i], Igor Paredes [j], Robert Webere [e], Margaret Turk [e], Jun Kimura [k,2,*], Jianyuan Jiang [a,2,*]

[a] Department of Orthopedics, Huashan Hospital, Fudan University Shanghai 200040, China
[b] Department of Orthopedics, The Fifth People's Hospital, Fudan University Shanghai 200240, China
[c] Department of Spine, Tianjin Hospital, Tianjin 300000, China
[d] Department of Orthopaedics, Peking University Third Hospital, Beijing 100191, China
[e] Department of Physical Medicine and Rehabilitation, Upstate University Hospital, Syracuse, NY 13210, USA
[f] Department of Neurology, School of Medicine, Chiba University Hospital, Chuo-ku, Chiba-shi, Chiba 260-8677, Japan
[g] NMR Research Unit, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK
[h] Department of Neurology, Jaypee Hospital, Sector 128, Noida UP – 201304, Delhi NCR, India
[i] Department of Neurosurgery, Tokyo Metropolitan Neurological Hospital, 2-6-1 Musashidai, Fuchu, Tokyo 183-0042, Japan
[j] Department of Neurosurgery, University Hospital 12 de Octubre, Av. Cordoba, s/n, 28041 Madrid, Spain
[k] Department of Neurology, University of Iowa Health Care, Iowa City, IA 52242, USA

ARTICLE INFO

Article history:
Accepted 11 February 2020
Available online 16 March 2020

Keywords:
Hirayama disease
Diagnosis
Treatment
Delphi technique
Clinician-led guideline

HIGHLIGHTS

- A modified 3-round Delphi survey resulted in a clinician-led guideline in Hirayama disease (HD).
- This is the first time to establish a clinician-led guideline for clinical practice in HD.
- Given lack of high-grade studies, this experts' guideline may provide a helpful direction for HD.

ABSTRACT

Objective: To establish a clinician-led guideline for the diagnosis and treatment of Hirayama disease (HD) using a modified Delphi technique.
Methods: Based on a combination of a systematic review and opinion of ten experts, a protocol for the consensus of the diagnosis, treatment and follow-up assessment of HD was established. A modified 3-round Delphi survey was then performed by more than 40 panelists from various countries of the world. Both levels of evidence and levels of agreement were derived in all statements of finial guideline.
Results: A total of 47 experts from 6 countries were enrolled in the expert panel in this study. Highly consistent results were achieved during the three Delphi rounds. An expert-led guideline finally constructed includes 24 statements related to diagnosis, treatment and follow-up assessment of HD.
Conclusions: The modified Delphi technique used in this study resulted in an expert-led guideline concerning several clinical aspects of HD.
Significance: This clinician-led guideline may provide a helpful direction for clinical practice with regard to the diagnosis and treatment of HD.

* Corresponding authors at: Department of Orthopedics, Huashan Hospital, Fudan University Address: Department of Orthopedics, Huashan Hospital, Fudan University. 12 Mid- Wulumuqi Road, Shanghai 200040. China. (J. JIANG). Department of Neurology, University of Iowa Health Care. Address: 200 Hawkins Drive, Iowa City, IA 52242, USA. (J. KIMURA).
E-mail addresses: kimurakyoto@aol.com (J. Kimura), Jianyuanjiang05@126.com (J. Jiang).
[1] These authors contributed equally to this work and should be considered co-first authors.
[2] These authors contributed equally to this work and should be considered co-corresponding author.

https://doi.org/10.1016/j.clinph.2020.02.022
1388-2457/

1. Introduction

Hirayama disease (HD), also referred to as juvenile muscular atrophy of the distal upper extremities, is a special neurological disorder first brought to attention by a Japanese neurologist, Keizo Hirayama (Hirayama, 2000a). HD is clinically characterized by unilateral or bilateral asymmetric amyotrophy of the hand and forearm muscles supplied by the C7-T1 myotomes, with sparing of the brachioradialis and proximal muscles of the upper limb innervated by C5-6 myotomes, without objective sensory disturbance or lower limb involvement (Hirayama, 2008; Huang et al., 2008; Zhou et al., 2010). Predominantly affecting male adolescents, HD also features obviously regional differences (Huang et al., 2008; Zhou et al., 2010; Hassan and Sahni, 2013). Most HD patients have characteristic abnormal forward-shifting of the posterior dura (crescent-shaped loss of attachment behind the posterior dura) during neck flexion in magnetic resonance imaging (MRI) (Hirayama, 2008; Hou et al., 2012; Fu et al., 2008), and both autopsy and neuropathologic studies demonstrated major lesion of HD occurred primarily in locations such as cervical anterior horn and ventral roots (Hirayama et al. 1987; Hirayama, 2000b; Imai et al., 2000; Zheng et al., 2017a). Therefore, ischemic injury of the cervical anterior horn and/or nerve root caused by the excessive forward displacement of the posterior dura during neck flexion has become the main current hypothesis of the pathogenicity mechanism of HD, and restricting neck flexion (e.g., neck collar support and surgical treatment) has become the main method of treating HD (Yang et al., 2014; Hassan et al., 2012; Ito et al., 2014; Guo et al., 2014).

In early studies, HD was recognized as a subtype of spinal muscular atrophy (SMA) and described as "juvenile asymmetric segmental spinal muscular atrophy" because of similar clinical manifestations (Peiris et al., 1989; Willeit et al., 2001). However, genetics studies demonstrated there is no survival motor neuron (SMN) gene deletion in HD patients compared with patients with SMA (Mishra et al., 2004; Misra et al., 2005), and both significant cervical structural abnormalities and relatively better clinical prognosis in HD further supported the difference between the two diseases. Therefore, clinicians established HD as a new entity that differs from SMA or other motor neuron disease (Hirayama 2008). However, this benign disease, if not treated early and reasonably, may cause serious dysfunction of bilateral upper limbs with loss of productivity. Unfortunately, both neck collar support and surgical treatment have only been applied in a small number of cases due to the lack of a criteria for the diagnosis and treatment of HD.

There are some important barriers impeding the establishment of an evidence-based guideline for the diagnosis and treatment of the patients with HD. Although many different diagnostic techniques involving clinical manifestation, imaging and electrophysiology are used to differentiate these two diseases in clinical, there is still a lack of reliable methods to distinguish HD from amyotrophic lateral sclerosis (ALS) in the early stage of the disease (Schroder et al., 1999; Zheng et al., 2017). Furthermore, it is difficult to identify whether the cessation of disease and the gradual improvement of the symptoms are ascribed to the medical intervention or to natural course (self-limitation). More importantly, although many studies have been conducted in HD during the past few decades, there are few enough numbers of high-grade studies to create an evidence-based guideline.

The Delphi technique originally employed in a series of studies that the RAND Corporation conducted in the 1950s (Maher et al., 2015). One of the main advantages of the Delphi technique is that it can accommodate knowledge gathering from a number of clinical experts in various geographical locations and different areas of expertise. As a consensus method, the Delphi technique was considered a more appropriate approach to remove these barriers in HD, and this specific technique has been used successfully in other diseases with similar diagnostic difficulty or therapeutic controversy, such as for thyroid eye diseases, idiopathic pulmonary fibrosis and septic shock (Maher et al., 2015; Cid et al., 2015; Douglas et al., 2009).

The primary aim of this study was to establish an expert-led guideline on the diagnosis and treatment of HD using a modified Delphi technique.

2. Methods:

2.1. Literature review

In this study, a structured literature review was conducted before performing the Delphi survey (Supplementary Fig. 1). A systematic review was conducted using both Medline and EMBASE, and all English language articles involving current opinion on the diagnosis, treatment and follow-up assessment for the patients with HD between January 1997 and January 2017 were retrieved.

In the first phase, all identified study titles were reviewed, and ineligible studies were excluded. Then, we reviewed the abstracts of both eligible studies and uncertain ones based on the titles in the second phase. In the third phase, the full papers of both eligible studies and uncertain ones based on the abstract were reviewed. The studies without full paper were excluded in this study. At last, all identified studies were listed, and the contents involving the diagnosis, treatments and follow-up assessment for HD were included in initial protocol.

Following completion of above-mentioned protocol, ten members in expert panel were invited to participate in exploring the results of the literature review and discussing additional items that might be appropriate for inclusion in statements, and then, initial statements were reviewed by the panel chairperson to confirm clinical accuracy before the first round of the Delphi technique.

2.2. Expert panel members

According to the literature search, the experts from several different areas of expertise, including neurology, spinal surgery, radiology, neurosurgery, hand surgery and rehabilitation, from all over the world were invited using e-mail or express. These experts should be the practicing clinicians working in their clinical field for at least 5 years, have a master's degree or higher qualification, and with experience in diagnosing and treating patients with HD. Finally, forty-seven respondents from China, the United States, Japan, India, Spain, and the United Kingdom were invited to be the panelists in this study (Table 1).

2.3. Delphi rounds

According to the previous study (Smolen et al., 2010; Cid et al., 2015), a modified Delphi technique was adopted for the clinician-led guideline establishment process in this study (Fig. 1).

In the first round, the questionnaire was e-mailed or express to every expert in the panel from May 2017 to July 2017 (Supplementary Table 1). A "yes" or "no" response was requested for each item in the questionnaire, and the participants were allowed to skip questions, indicating insufficient knowledge or experience. They were also invited to provide additional suggestions at the end of every section of the questionnaire. Items supported by $\geq$75% (3/4) of the experts were enrolled while <25% (1/4) were eliminated. The remaining items were modified and subjected to the next round.

Table 1
Demographic characteristics of the Delphi panel.

	Round 1 questionnaire (n = 47)	Round 2 questionnaire (n = 46)	Face-to-face meeting (n = 42)
Gender			
female	15	15	14
male	32	31	28
Age			
<45	9	9	8
45–55	22	21	19
>55	16	16	15
Years in practice			
<10	5	5	5
10–30	22	21	18
>30	20	20	19
Education background			
Doctor's degree	23	22	20
Master's degree	24	24	22
Professional job title			
Chief physician	5	5	4
Associate chief physician	13	12	12
Attending physician	29	29	26
HD patients treated			
<10	11	10	10
10–50	15	15	12
>50	21	21	20

HD: Hirayama diseasen.
n: the number of the panelists who attended the questionnaire or meeting.

The second round took place from December 2017 to January 2018 with a questionnaire based on the experts' feedback on the round 1 questionnaire (Supplementary Table 2). A report demonstrating the result of the round 1 questionnaire was also provided with the second questionnaire through the e-mail or express. A "yes" or "no" response and additional suggestions were also requested in this round. Items achieved over 67% (2/3) agreement were accepted and the remnants were revised and subjected to face-to-face discussion.

In the third round, we dealt with the items that achieved no consensus during the first and second rounds through face-to-face meeting (April 2018) (Supplementary Table 3). Experts were invited to express individual opinions on each item under consideration followed by a brief discussion led by a facilitator. Subsequently, each expert provided a "yes" or "no" response, and a majority of ≥50% (1/2) was required for the enrolled items. Finally, all panelists voted on the level of agreement with each enrolled item in this consensus using a 10-point numerical rating scale (1 = do not agree at all, 10 = agree completely).

The statements were then sent by email or express for final comments. Only suggestions for improvements of clarity of wording or removal of redundancies were considered. Proposed changes to the meaning were not accepted, although they will be mostly dealt with in the comments to each item.

3. Results

In this study, the structured systematic review identified 33 articles that involves the diagnosis and treatment of HD between 1997 and 2017, and the results of the literature review indicated there was little consensus or agreement on treatment in HD. Furthermore, there were contradictory opinions regarding the diagnosis in HD, with some suggesting the there is no significant difference in either MRI or electrophysiological findings in HD between the neck standard and flexion position (Schroder et al.,1999; Willeit et al., 2001; Misra et al.,2006; Ammendola et al. 2008). Forty-seven experts participated in this study, representing 6 countries (China, the United States, Japan, India, Spain, and the United Kingdom) and 6 areas of expertise (neurology, spinal surgery, neurosurgery, hand surgery, rehabilitation and radiology). All these 47 panelists completed the first-round questionnaire, and 46 of these 47 experts completed the second-round questionnaire. In the third round, 42 of these 47 panelists attended the face-to-face meeting.

The first-round questionnaire consisted of 29 items, including the diagnosis, the treatment and the follow-up assessment (Supplementary Table 1). Of this, 6 achieved consensuses (agreement ≥ 75%) in this round while 7 were excluded (agreement < 25%). Therefore, the other 16 items in the first-round questionnaire were revised for the second-round questionnaire, and 2 of these 16 items (No. 3 and 6 items in the first-round questionnaire) were respectively divided into two items in order to facilitate a clearer understanding for the reader (Supplementary Table 2). Furthermore, nine new items were identified in the additional suggestions, and all of these 9 items were reviewed by the panel chairperson and added to the next questionnaire (Supplementary Table 2). Thus, twenty-seven items were reviewed in the second round (Supplementary Table 2).

In the second round, we achieved consensus on 9 items (agreement ≥ 67%), and the remaining 18 items (agreement < 67%) were to discuss in the next round.

In the third round, these 18 remaining items were reviewed, and 9 of these 18 items achieved consensus (agreement ≥ 50%) (Supplementary Table 3). Furthermore, all items were also revised to enhance clarity in this face-to-face meeting according to the opinion of the panelists.

The consensus constructed based on the results of three Delphi rounds is listed in Table 2, along with the percentage of panelists who voted for each statement in Table 3. For all statements, the levels of evidence range from Level I (high quality randomized controlled trial) to Level V (expert consensus) have been determined in accordance with the systematic literature review and are mentioned in Table 3, and the levels of evidence used in this study mainly referred to the previous literature (Supplementary Table 4) (Bono et al., 2011). Furthermore, the level of agreement as determined during the final face-to-face meeting is provided (Table 3), and the level of agreement ranged from 8.8 to 10.0 on a 10-point scale.

4. Discussion

Based on a combination of a systematic literature review and expert opinion, 24 statements were included in the final consensus statements in this study. In terms of this guideline, although most statements are supported by evidence-based clinical research, some important and meaning statements are mainly expert-based.

The previous study demonstrating significant correlation between the age when the body height increased most rapidly and the onset age of HD (Toma and Shiozawa, 1995). Thus, the disproportionate growth of cervical spine and cervical cord/roots has been widely considered as the pathophysiological basis of HD, which was further supported by subsequent studies (Kohno et al., 1998; Zheng et al., 2017a). This hypothesis provides a reasonable explanation for that HD always starts in adolescence. More importantly, compared with the female, both annual body height growth and the slope of the growth velocity curve are significantly larger in males (Toma and Shiozawa, 1995). Therefore, women are rarely afflicted with HD. All of these studies and previous nationwide survey of HD in japan further supported that HD is an adolescence- and male-prone disorder (Tashiro et al., 2006) (statement #1, Level III). Furthermore, different growth rate of bilateral arms can also be used to explain why the symptoms (including atrophy, weakness, and denervation) are generally asymmetrical in most patients with HD in many previous studies (Peiris et al.,

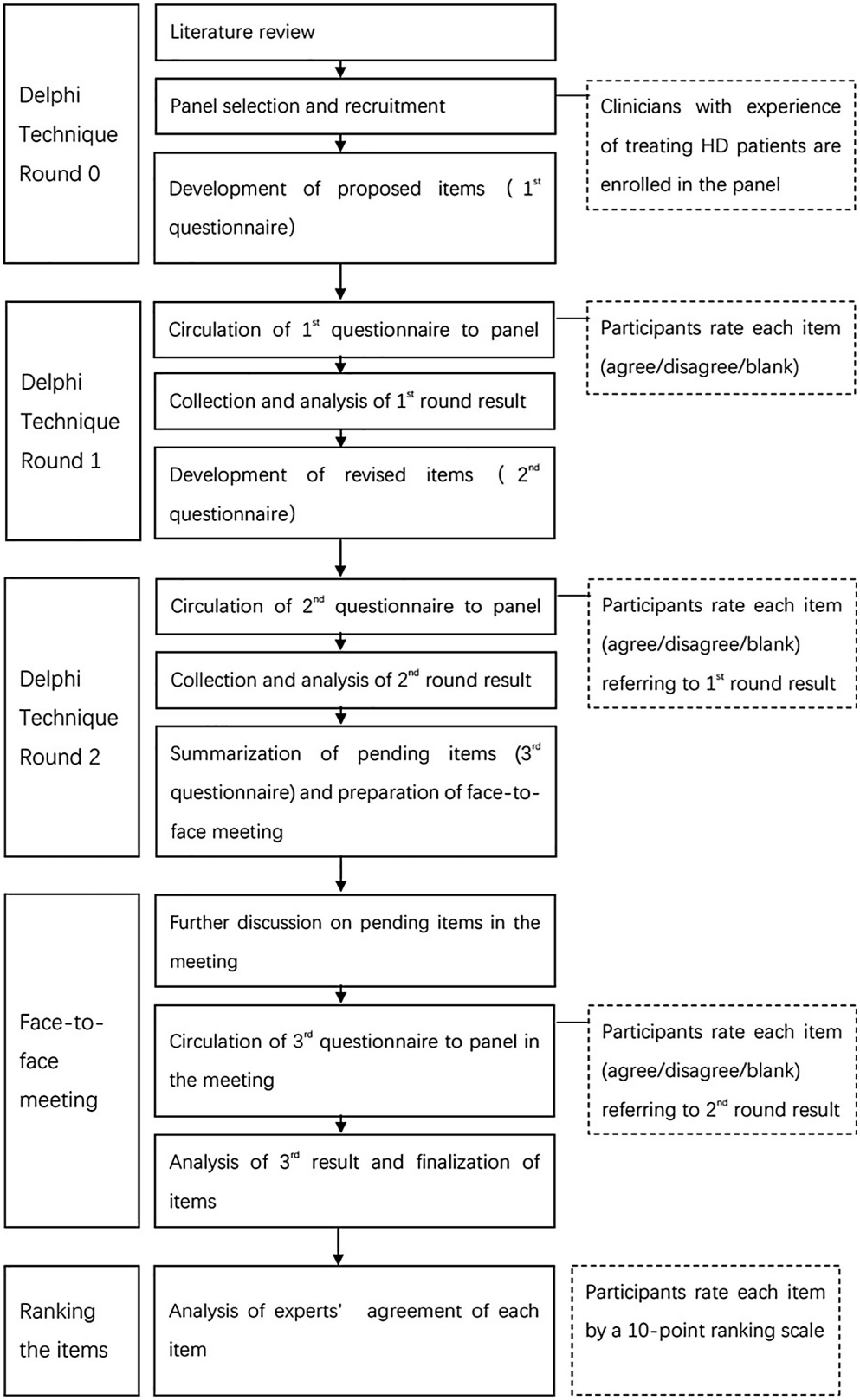

Fig. 1. Specific flow chart for the modified Delphi method used in this study. HD: Hirayama disease.

1989; Kao et al., 1993; Gourie-Devi M and Nalini A, 2003; Guo et al., 2012) (statement #9, Level IV). Another possible reason for the male preponderant in HD is the role of the X chromosome (Mishra et al., 2004; Misra et al., 2005; Hommel et al., 2016), and some familial male cases have been reported (Schlegel et al., 1987; Andreadou et al., 2009; Kajikawa et al., 2009). Considering that familial forms of HD are very rare, which may need further evaluation.

Table 2
Expert-led guideline.

Domain	Items
Clinical features for diagnosis	
	1. HD predominately develop in Asian male adolescents (younger than 20 years). 2. HD may gradually slow down and become self-limited after 2–5 years of disease onset. 3. Some patients with HD may experience repeated disease progression with an interval of stable stage. 4. The diseases duration may last for more than 5 years in some patients with HD. 5. The muscle atrophy of HD is confined to the upper limbs, predominately involving the intrinsic muscles of hand and forearm muscle group. 6. The muscular atrophy of hand muscles in the patients with HD is predominant in ulnar side, reverse split hand syndrome. * 7. The oblique amyotrophy due to atrophy involves the medial, volar and dorsal surfaces of the forearm, sparing the brachioradialis muscle, is the typical clinical manifestation of HD. *$ 8. Other clinical symptoms including cold paresis, tremor on finger extension, and muscular fasciculation can occur in some patients with HD. & 9. The symptoms (including atrophy, weakness, and denervation) are generally asymmetrical in most patients with HD. 10. A small number of patients with HD may experience subjective paresthesia in upper limbs during the early stages. 11. In the majority of HD patients, the pyramidal tract signs do not exist. If pyramidal tract signs are found, regular follow-up is suggested to rule out the possibility of motor neuron disease.
Auxiliary examinations for diagnosis	
	12. The anterior shifting of the posterior dura and crescent-shaped high signal posterior to dura in neck-flexion MRI is one of the most essential evidence for diagnosis of HD. * 13. The cervical spinal cord atrophy, snake eyes sign, and abnormal high signal in the spinal cord may also be seen in the neck-standard MRI findings of the patients with HD. # 14. The dynamic enhanced MRI is more contributive to the diagnosis of Hirayama disease. 15. Dynamic X-ray of cervical vertebra may be used for differential diagnosis of HD. 16. Electrophysiological examinations are indispensable for the diagnosis of HD.
Treatment	
	17. Long-time cervical collar treatment is an optional conservative treatment. 18. Neurotrophic drug can be used in the conservative treatment. 19. It is reasonable to conduct surgical treatment in at least one of the following circumstances: a) the disease keeps progressing after long-time wearing cervical collar; b) the patients with HD cannot bear the long time wearing cervical collar; c) the disease progresses again after the spontaneous arrest. 20. Anterior cervical fusion procedure is an appropriate operation mode. 21. Posterior cervical duraplasty is an appropriate operation mode. 22. There is no convincing evidence to prove which optional operation mode is better. Both anterior fixation and posterior duraplasty are optional operation modes.
Follow-up assessment	
	23. Motor unit number estimation is suitable for the follow-up evaluation of the patients with HD. 24. Needle EMG examination (esp. recruitment and denervation changes) is suitable for the follow-up evaluation of the patients with HD.

HD: Hirayama disease; MRI: Magnetic resonance imaging; EMG: Electromyography
*: the clinical features and dynamic MRI findings were mentioned in the supplementary Figure 2.
#: the imaging features of neck-standard MRI were mentioned in the supplementary Figure 3.
$: Oblique amyotrophy: The pattern of atrophy mainly involves the medial, volar and dorsal surfaces of the forearm, sparing the brachioradialis muscle (supplementary Figure 2).
&: Cold paresis: Patients with HD often presented with transient aggravation of muscle weakness in the affected muscles with exposure to cold.

Table 3
Levels of evidence, agreement, and votes for each item.

Item	Levels of evidence	Level of agreement	Percentage of votes (round of enrollment)
1	III	10	93.62%(1)
2	III	9.52	91.49%(1)
3	V	9.81	61.90%(3)
4	V	9.33	69.05%(3)
5	IV	9.57	73.91%(2)
6	III	9.76	86.96%(2)
7	III	9.71	69.57%(2)
8	III	9.81	82.98%(1)
9	IV	9.86	78.26%(2)
10	IV	9.86	71.74%(2)
11	V	9.81	82.61%(2)
12	III	9.86	84.78 %(2)
13	IV	9.81	89.36%(1)
14	V	9.86	78.72%(1)
15	IV	9.76	66.67%(3)
16	III	9.81	89.36%(1)
17	III	9.38	71.43%(3)
18	V	8.81	69.57%(2)
19	V	9.86	73.91%(2)
20	III	9.38	73.81%(3)
21	III	9.33	66.67%(3)
22	V	9.81	80.95%(3)
23	IV	9.71	61.90%(3)
24	V	9.33	57.14%(3)

In the last two decades, the number of cases reports involving HD in areas other than Asia has significantly increased (Elsheikh et al., 2009; (Ghosh et al., 2011); Finsterer et al., 2013; Lehman et al., 2013; Cortese et al., 2015). Furthermore, all HD patients in the study of Ghosh et al. were misdiagnosed initially, suggesting previously lower incidence of HD in Europe and America areas may be ascribed to the lack of the awareness of this disease (Ghosh et al., 2011). Therefore, HD may be not uncommon in the areas other than Asia. However, according to the current literatures from both Asia and other areas (Elsheikh et al., 2009; (Ghosh et al., 2011)), HD is still more common in Asian countries, and this statement (#1) was also recognized by almost all experts in this study including the ones from both North America and Europe.

While it is widely accepted that HD is a self-limited disease according to the previous studies (Gourie-Devi M and Nalini A, 2003; Tashiro et al., 2006; Huang et al., 2008) (statement #2, Level III), both statements #3 and #4 received high votes and levels of agreement and suggested that HD may not be self-limited or need a longer time than expected to stop progressing (statements #3 and #4, Level V). These statements are also supported by some circumstantial evidences as follows: a case-series study indirectly reports that approximately 7.5% of patients with HD may exhibit disease progression over 5 years (Huang et al., 2008), and it is confirmed that the disease still advances in two HD patients with disease duration more than 10 years in previous case reports (Ciceri et al. 2010; Li, 2012).

According to the previous autopsy studies (Hirayama et al., 1987; Hirayama, 2000b), major lesion sites of HD are located in

the cervical anterior horn and ventral root (Tokumaru and Hirayama, 1994). Therefore, almost experts agreed that the muscle atrophy of HD is confined to the upper limbs (statement #5, level IV) and there is no objective sensory disturbance (including neurological examination and traditional nerve conduction studies) in patients with HD, although some previous studies demonstrated there is mild difference of electrophysiological detection in sensory nerves between the healthy subjects and the HD patients (Liao et al., 2005; Polo et al., 2003). However, some experts raised that some HD cases may experience paresthesia in the involved side at the early stages of disease, which was further reported in some previous studies (Huang et al., 2008; Hirayama et al., 1987; Kao et al., 1993; Tynan et al., 2010). Therefore, the revisions were made to the statement involving abnormal sensation in HD to clarify that "a small number of patients" rather than "no patients" had "subjective" sensory abnormalities (statement #10, Level IV).

Dissociated wasting of the hand and forearm muscles supplied by C7-T1 myotomes with relative preservation of the brachioradialis muscles supplied by C5-6 myotomes is a specific clinical feature of HD (statement #7, Level III) (Hirayama et al., 1987; Hirayama, 2000a; Wang et al., 2012; Supplementary Figure 2). More importantly, significant wasting of the median-side hand muscles with relative preservation of ulnar-side hand muscles was identified in the patients with HD (Lyu et al., 2011; Jin et al. 2014) (statement #6, Level III), although both muscles are innervated by C8-T1. One possible explanation for this pattern of hand muscle involvement in HD is the discrete arrangement of nerve fibers supplying the medial and lateral hand muscles at the C8-T1 segments, and partial compressive or ischemic lesions may preferentially damage nerve fibers supplying the medial hand muscle in HD patients (Zheng et al., 2017d). Contrary to cortical origin of split hand syndrome in ALS, Lyu et al. surmised the pattern of hand muscle involvement in HD, namely reverse split hand syndrome, may be of spinal origin (Lyu et al., 2011). Therefore, HD is primarily a lower motor neuron (LMN) disease that may be another possibility.

Although some previous studies demonstrated that HD patients with long disease duration may develop cervical cord injury with disease progression (Misra and Kalita, 1995; Zheng et al., 2017c), most panelist considered the pyramidal tract signs do not exist in the majority of HD patients since more studies, especially the previous autopsy studies, confirm that HD is a disorder involving lesion of LMN (Hirayama et al., 1987; Hirayama, 2000b; Lyu et al., 2011). Therefore, if patients who have been diagnosed as HD through clinical features and auxiliary examinations listed in this expert-led guideline presented with pyramidal tract signs, regular follow-up is suggested to rule out the possibility of motor neuron disease (statement #11, Level V).

Similar to the oblique amyotrophy (Supplementary Figure 2), cold paresis (transient aggravation of muscle weakness in the affected muscles with exposure to cold), tremor on finger extension and muscular fasciculation are common in patients with HD (statement #8, Level III) (Sobue et al., 1978; Singh et al., 1980; Tan, 1985; Peiris et al., 1989; Kao et al., 1993; Hirayama, 2000a; Huang et al., 2008). The previous study demonstrated the incidence rate of cold paresis and tremor on finger extension is respectively 27.3–97% and 8.5–88.9% (Sobue et al., 1978; Singh et al., 1980; Tan, 1985; Peiris et al., 1989; Kao et al., 1993; Hirayama, 2000a; Huang et al., 2008). Gourie-Devi and Nalini demonstrated cold paresis may be ascribed to sympathetic dysfunction (Gourie-Devi and Nalini, 2001), and altered axonal excitability may be another possible reason for this phenomenon (Sawai et al., 2011).

In the previous studies, abnormal forward displacement of the cervical cord during neck flexion in dynamic MRI or computed tomography myelography (CTM) was demonstrated to be a specific imaging manifestation of HD (statement #12, Level III) (Hirayama, 2008; Hou et al., 2012; Fu et al., 2008; Supplementary Figures 2 and 3). However, similar neuroradiological abnormalities have been found in normal subjects (Schroder et al., 1999), and some patients with identified HD but without significant dynamic imaging abnormalities were also reported in some case reports (Schroder et al., 1999; Willeit et al., 2001). In addition, some recently published studies have shown that both neck-standard MRI findings (e.g., cervical cord atrophy and abnormal high signal) and dynamic X-ray can also contribute to the diagnosis and differential diagnosis of HD (Supplementary Figure 3) (Li and Remmel, 2012; Lai et al., 2011; Xu et al., 2011), which were mentioned in the statements #13 and #15 (Level III). Therefore, abnormal forward displacement of the cervical cord (loss of attachment) in neck-flexion MRI should be "one of the most essential evidence for diagnosis" rather than "the indispensable findings for the diagnosis". Furthermore, the loss of attachment in HD may be mainly ascribed to the congestion of the posterior epidural venous plexus (Elsheikh et al., 2009). Therefore, Expert panel considered that enhanced MRI is more contributive to the diagnosis of HD (statement #14, Level V).

According to the previous studies (Behnia and Kelly, 1991; Huang et al., 2008; de Carvalho et al., 2008; Guo et al., 2014), denervation and reinnervation confined to the upper limbs identified by needle electromyogram (EMG) detection is important evidence for distinguishing HD from other similar diseases [e.g., ALS and multifocal motor neuropathy (MMN)]. However, needle EMG features of the early stage of ALS may be similar to the HD. Thus, needle EMG follow-up assessment is necessary for the patients with uncertain diagnosis of HD. Furthermore, both compound muscle action potential (CMAP) decrement to repetitive nerve stimulation and split-hand phenomenon quantified by CMAP amplitude were demonstrated to be useful in distinguishing ALS and HD, even in the early stages (Jin et al., 2014; Lyu et al., 2011; Zheng et al., 2017). Therefore, electrophysiological examinations are indispensable for the diagnosis of HD (statement #16, Level III).

As the major conclusion, both neck collar support and neurotrophic pharmacological treatment were accepted as the conservative treatment for HD in this consensus. In the previous studies, both Imai et al. and Hassan et al. demonstrated that the effectiveness of cervical collar therapy in preventing the dynamic damage of the cervical motor neurons in HD (Imai et al., 2000; Hassan et al., 2012). Therefore, long-time cervical collar treatment may be an optional conservative treatment for HD (statement #17, level III). Furthermore, the literatures in the systematic review in this study included numerous reports describing the different treatments of patients with HD. Although none of these reports described the effect of neurotrophic pharmacological treatment in patients with HD, it is the consensus of the expert panel that clinical experience indicates that neurotrophic drugs may be helpful in the treatment of HD (statement #18, level V).

Although compared with both cervical collar therapy and neurotrophic pharmacological treatment, surgical treatment has relatively large risks mainly due to the similarity between HD and ALS, the expert panel felt that, while being an important alternative treatment, cervical collar therapy is not suitable to the patients with HD who have relapsed or protracted course of diseases. A large number of previous studies have confirmed the effectiveness of surgical treatment for HD (Konno et al., 1977; Lu et al., 2013; Ito et al., 2014; Agundez et al., 2015; Brandicourt et al., 2018), and recently published studies further demonstrated relatively better treatment outcome of both anterior cervical fusion procedure and posterior cervical duraplasty compared to the non-surgical

treatment (Ito et al., 2014; Zheng et al., 2018) (statements #20, Level III; statements #21, Level III). Unfortunately, in the absence of reliable evidence, it is the expert panel's opinion that both anterior fixation and posterior duraplasty are optional operation modes (statements #21, Level V). Furthermore, according to the opinions of expert panel, we further got the surgical indications of the patients with HD in this consensus (statement #19, Level V), and some of these surgical indications was supported by recent retrospective analysis of a large cohort (Song et al., 2017). More importantly, these statements involving surgical treatment received high level of agreement, which implies a broad international recognition and consensus since the members in the expert panel came from so many different countries of the world and areas of expertise.

HD progressed slowly with insidious onset, and most patients with HD may become self-limiting at last (Hirayama, 2000a; Hirayama 2008). Therefore, it is difficult to identify whether the cessation of disease and the gradual improvement of the symptoms are ascribed to the treatment or to natural course (self-limitation). Unfortunately, the expert panel was almost unanimous that conventional scoring scales cannot effectively evaluate the cessation of HD progression in both first and second rounds. Therefore, some experts raised both motor unit number estimation (MUNE) and needle EMG examination (esp. recruitment and denervation changes) may be feasible and useful for the follow-up assessment, and the validity of MUNE for tracking the progression of HD in a clinical setting was further confirmed by the recently published paper (Zheng et al., 2017d). More importantly, both statements were agreed in the finial face-to-face meeting (Statement #23 Level IV; Statement #24, Level V).

Although Delphi method may have some shortcomings because of its inherent procedures, this method is a relatively rigorous consensus methodology and may be an appropriate approach to solve the lack of enough number of high-grade studies in both the diagnosis and treatment of HD. This Delphi surveys included many clinicians from Asia, which may limit the application of this consensus. However, as the number of the clinicians treating HD is small, and HD is mostly distributed in Asian countries. Therefore, the composition of the expert panel is considered reasonable. Furthermore, many important problems remained unresolved in this Delphi study [e.g., which operation mode may be more suitable for the patients with HD (Ito et al., 2014; Lu et al., 2013), whether the pyramidal tract signs might occur in some HD patients (Zheng et al., 2017a).], which may be ascribed to lack of the cross-impact analysis in this study. However, similar modified Delphi method without cross-impact analysis used in this study has already been successfully employed in some previous studies (Smolen et al., 2010; Cid et al., 2015; Zang et al., 2015), and the aspects with no consensuses may represent important research areas for future work.

The results of this study should be interpreted with caution. It is important to note that both diagnosis and treatment which the panelists reached the consensus may not improve the clinical outcomes without evidence form high-level clinical trials. Furthermore, this expert-led guideline does not represent a standard of diagnosis and treatment, and both diagnosis and treatment should be based on the individual patient's need and physician's professional judgment. It is also acknowledged there will be atypical patients who will require less or more methods of diagnosis and treatment outside this expert-led guideline.

5. Conclusion

Using a modified Delphi technique, the final 24 statements included the diagnosis (clinical features and auxiliary examinations), treatment (conservative and surgical treatment) and follow-up assessment of HD, and this clinician-led guideline may be currently used to guide clinical practice with regard to the diagnosis and treatment of HD until high-grade evidence-based guidelines are finished in the future.

Acknowledgments

Financial support from Shanghai City Health System of the Second Batch of Important Diseases Combined Project (2014ZYJ0008) and the National Natural Science Foundation of China Youth Science Foundation Project (81501909) are gratefully acknowledged.

We would like to thank **Dr. Chen Shuang** (Radiology, Fudan University Huashan Hospital, Shanghai, China), **Dr. Fu Yu** (Neuro logy, Peking University Third Hospital, Beijing, China), **Dr. Guan Yuzhou** (Neurology, Beijing Union Medical Collage Hospital, Beijing, China), **Dr. Jiang Congyu** (Rehabilitation, Fudan University Huashan Hospital, Shanghai, China), **Dr. Lu Jiahong** (Neurology, Fudan University Huashan Hospital, Shanghai, China), **Dr. Lin Jianhua** (Orthopedics, Fujian Medical University First Hospital, Fuzhou, Fujian Province, China), **Dr. Li Jianhua** (Rehabilitation, Sir Run Run Shaw Hospital Affiliated to Zhejiang University, Hangzhou, Zhejiang Province, China), **Dr. Liu Mingsheng** (Neurology, Beijing Union Medical Collage Hospital, Beijing, China), **Dr. Li Yuxin** (Radiology, Fudan University Huashan Hospital, Shanghai, China), **Dr. Li Feng** (Orthopedics, Tongji Medical College of HUST, Wuhan, Hubei Province, China), **Dr. Lyu Guohua** (Spine Surgery, the Second Hospital of Xiangya, Changsha, Hunan Province, China), **Dr. Li Wenjun** (Hand Surgery, Beijing Jishuitan Hospital, Beijing, China), **Dr. Lu Zuneng** (Neurology, Hubei Provincial People's Hospital, Wuhan, Hubei Province, China), **Dr. Ma Xun** (Orthopedics, the Second Affiliated Hospital of Shan Xi Medical University, Taiyuan, Shanxi Province, China), **Dr. Ni Bin** (Orthopedics, Chang Zheng Hospital, Shanghai, China), **Dr. Pan Shengfa** (Orthopedics, Peking University Third Hospital, Beijing, China), **Dr. Qiao Kai** (Neurology, Fudan University Huashan Hospital, Shanghai, China), **Dr. Qiao Hui** (Neurosurgery, Beijing Tian Tan Hospital, Capital Medical University, Beijing, China), **Dr. Tian Dong** (EMG Laboratory, Fudan University Huashan Hospital, Shanghai, China), **Dr. Wu Yi** (Rehabilitation, Fudan University Huashan Hospital, Shanghai, China), **Dr. Wang Huan** (Spine Surgery, Shengjing Hospital of China Medical University, Shenyang, Liaoning Province, China), **Dr. Xie Qing** (Rehabilitation, Ruijin Hospital, Medical College of Shanghai Jiao Tong University, Shanghai, China), **Dr. Xu Lei** (Hand Surgery, Fudan University Huashan Hospital, Shanghai, China), **Dr. Xia Hong** (Orthopedics, Guangzhou Military District General Hospital, Guangzhou, Guangdong Province, China), **Dr. Yao Weiwu** (Radio logy, Shanghai Sixth People's Hospital, Shanghai, China), **Dr. Yuan Wen** (Orthopedics, Chang Zheng Hospital, Shanghai, China), **Dr. Zhang Wenming** (Orthopedics, Fujian Medical University First Hospital, Fuzhou, Fujian Province, China), **Dr. Zhao Chongbo** (Neurology, Fudan University Huashan Hospital, Shanghai, China), **Dr. Zhou Feifei** (Orthopedics, Peking University Third Hospital, Beijing, China), **Dr. Zou Zhangyu** (Neurology, Union Hospital Affiliated to Fujian Medical University, Fuzhou, Fujian Province, China), **Dr. Zhu Qingsan** (Orthopedics, Jilin University Japan-China Union Hospital, Changchun, Jilin Province, China), **Dr. Zhu Yi** (EMG Laboratory, Fudan University Huashan Hospital, Shanghai, China), for their help during manuscript preparation.

Conflict of interest

The authors report no conflict of interest. The authors alone are responsible for the content and writing of this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinph.2020.02.022.

References

Agundez M, Rouco I, Barcena J, Mateos B, Barredo J, Zarranz JJ. Hirayama disease: Is surgery an option?. Neurologia. 2015;30:502–9.

Ammendola A, Gallo A, Iannaccone T, Tedeschi G. Hirayama disease: three cases assessed by F wave, somatosensory and motor evoked potentials and magnetic resonance imaging not supporting flexion myelopathy. Neurol Sci Off J Ital Neurol Soc Ital Soc Clin Neurophysiol. 2008;29:303–11.

Andreadou E, Christodoulou K, Manta P, Karandreas N, Loukaidis P, Sfagos C, et al. Familial asymmetric distal upper limb amyotrophy (Hirayama disease): report of a Greek family. Neurologist. 2009;15:156–60.

Behnia M, Kelly JJ. Role of electromyography in amyotrophic lateral sclerosis. Muscle Nerve. 1991;14:1236–41.

Bono CM, Ghiselli G, Gilbert TJ, Kreiner DS, Reitman C, Summers JT, et al. An evidence-based clinical guideline for the diagnosis and treatment of cervical radiculopathy from degenerative disorders. Spine J. 2011;11:64–72.

Brandicourt P, Sol JC, Aldéa S, Bonneville F, Cintas P, Brauge D. Cervical laminectomy and micro resection of the posterior venous plexus in Hirayama disease. Neurochirurgie. 2018;64:303–9.

Ciceri EF, Chiapparini L, Erbetta A, Longhi L, Cicardi B, Milani N, et al. Angiographically proven cervical venous engorgement: a possible concurrent cause in the pathophysiology of Hirayama's myelopathy. Neurol Sci. 2010;31:845–8.

Cid J, De La Calle JL, Lopez E, Del Pozo C, Perucho A, Soledad Acedo M, et al. A Modified Delphi Survey on the Signs and Symptoms of Low Back Pain: Indicators for an Interventional Management Approach. Pain Pract. 2015;15:12–21.

Cortese R, Gerevini S, Dicuonzo F, Zoccolella S, Simone IL. Hirayama disease: the importance of an early diagnosis. Neurol Sci. 2015;36:1049–50.

de Carvalho M, Dengler R, Eisen A, England JD, Kaji R, Kimura J, et al. Electrodiagnostic criteria for diagnosis of ALS. Clin Neurophysiol. 2008;119:497–503.

Douglas RS, Tsirbas A, Gordon M, Lee D, Khadavi N, Garneau HC, et al. Development of Criteria for Evaluating Clinical Response in Thyroid Eye Disease Using a Modified Delphi Technique. Arch Ophthalmol. 2009;127:1155–60.

Elsheikh B, Kissel JT, Christoforidis G, Wicklund M, Kehagias DT, Chiocca EA, et al. Spinal Angiography and Epidural Venography in Juvenile Muscular Atrophy. Muscle Nerve. 2009;40:206–12.

Finsterer J, Löscher W, Wanschitz J, Baumann M, Quasthoff S, Grisold W. Hirayama disease in Austria. Joint Bone Spine. 2013;80:503–7.

Fu Y, Pei X, Zhang J, Kang D, Han H, Fan D. Morphological changes of the lower cervical spinal cord under neutral and fully flexed position by MRI in Chinese patients with Hirayama's disease. Amyotroph Lateral Scler. 2008;9:156–62.

Ghosh PS, Moodley M, Friedman NR, Rothner AD, Ghosh D. Hirayama disease in children from North America. J Child Neurol. 2011;26:1542–7.

Gourie-Devi M, Nalini A. Long-term follow-up of 44 patients with brachial monomelic amyotrophy. Acta Neurol Scand. 2003;107:215–20.

Gourie-Devi M, Nalini A. Sympathetic skin response in monomelic amyotrophy. Acta neurologica scandinavica 2001;104:162–6.

Guo X, Lu M, Xie N, Guo Q, Ni B. Multilevel Anterior Cervical Discectomy and Fusion With Plate Fixation for Juvenile Unilateral Muscular Atrophy of the Distal Upper Extremity Accompanied by Cervical Kyphosis. J Spinal Disord Tech. 2014;27:E241–6.

Guo XM, Qin XY, Huang C. Neuroelectrophysiological characteristics of Hirayama disease: report of 14 cases. Chin Med J. 2012;125:2440–3.

Hassan KM, Sahni H, Jha A. Clinical and radiological profile of Hirayama disease: a flexion myelopathy due to tight cervical dural canal amenable to collar therapy. Ann Indian Acad Neurol. 2012;15:106–12.

Hassan KM, Sahni H. Nosology of juvenile muscular atrophy of distal upper extremity: from monomelic amyotrophy to Hirayama disease–Indian perspective. BioMed Res Int. 2013;2013 478516.

Hirayama K. Juvenile muscular atrophy of distal upper extremity (Hirayama disease): focal cervical ischemic poliomyelopathy. Neuropathology. 2000a;20:S91–4.

Hirayama K. Juvenile muscular atrophy of unilateral upper extremity (Hirayama disease) - half-century progress and establishment since its discovery. Brain Nerve Tokyo 2008;60:17–29.

Hirayama K. Juvenile muscular atrophy of distal upper extremity (Hirayama disease). Intern Med. 2000b;39:283–90.

Hirayama K, Tomonaga M, Kitano K, Yamada T, Kojima S, Arai K. Focal Cervical Poliopathy Causing Juvenile Muscular-Atrophy of Distal Upper Extremity - a Pathological-Study. J Neurol Neurosurg Psychiatry. 1987;50:285–90.

Hommel AL, Jewett T, Mortenson M, Caress JB. Juvenile muscular atrophy of the distal upper extremities associated with x-linked periventricular heterotopia with features of Ehlers-Danlos syndrome. Muscle Nerve. 2016;54:794–7.

Hou C, Han H, Yang X, Xu X, Gao H, Fan D, et al. How does the neck flexion affect the cervical MRI features of Hirayama disease?. Neurol Sci. 2012;33:1101–5.

Huang YC, Ro LS, Chang HS, Chen CM, Wu YR, Lee JD, et al. A clinical study of Hirayama disease in Taiwan. Muscle Nerve. 2008;37:576–82.

Imai T, Shizukawa H, Nakanishi K, Kouge N, Hiura K, Kashiwagi M, et al. Hyperexcitability of cervical motor neurons during neck flexion in patients with Hirayama disease. Electromyogr Clin Neurophysiol. 2000;40:11–5.

Ito H, Takai K, Taniguchi M. Cervical duraplasty with tenting sutures via laminoplasty for cervical flexion myelopathy in patients with Hirayama disease: successful decompression of a "tight dural canal in flexion" without spinal fusion. J Neurosurg Spine. 2014;21:743–52.

Jin X, Jiang JY, Lu FZ, Xia XL, Wang LX, Zheng CJ. Electrophysiological differences between Hirayama disease, amyotrophic lateral sclerosis and cervical spondylotic amyotrophy. BMC Musculoskelet Disord. 2014;15:349.

Kajikawa H, Kokubo Y, Taniguchi A, Naito Y, Kuzuhara S. Juvenile muscular atrophy of the distal upper extremity (hirayama disease) in two lanky look-alike brothers. Neurologist 2009;15:220–2.

Kao KP, Wu ZA, Chern CM. Juvenile lower cervical spinal muscular atrophy in Taiwan: report of 27 Chinese cases. Neuroepidemiology 1993;12:331–5.

Kohno M, Takahashi H, Yagishita A, Tanabe H. "Disproportion theory" of the cervical spine and spinal cord in patients with juvenile cervical flexion myelopathy. A study comparing cervical magnetic resonance images with those of normal controls. Surg Neurol. 1998;50:421–30.

Konno S, Goto S, Murakami M, Mochizuki M, Motegi H, Moriya H. Juvenile amyotrophy of the distal upper extremity: pathologic findings of the dura mater and surgical management. Spine 1977;22:486–92.

Lai V, Wong YC, Poon WL, Yuen MK, Fu YP, Wong OW. Forward shifting of posterior dural sac during flexion cervical magnetic resonance imaging in Hirayama disease: an initial study on normal subjects compared to patients with Hirayama disease. Eur J Radiol. 2011;80:724–8.

Lehman VT, Luetmer PH, Sorenson EJ, Carter RE, Gupta V, Fletcher GP, et al. Cervical spine MR imaging findings of patients with Hirayama disease in North America: a multisite study. AJNR Am J Neuroradiol. 2013;34:451–6.

Liao JP, Waclawik AJ, Lotz BP. Subclinical sensory involvement in monomelic amyotrophy. J Clin Neuromuscul Dis. 2005;7:66–9.

Li Y, Remmel K. A case of monomelic amyotrophy of the upper limb: MRI findings and the implication on its pathogenesis. J Clin Neuromuscul Dis. 2012;13:234–9.

Lu F, Wang H, Jiang J, Chen W, Ma X, Ma X, et al. Efficacy of anterior cervical decompression and fusion procedures for monomelic amyotrophy treatment: a prospective randomized controlled trial Clinical article. J Neurosurg-Spine. 2013;19:412–9.

Lyu RK, Huang YC, Wu YR, Kuo HC, Ro LS, Chen CM, et al. Electrophysiological features of Hirayama disease. Muscle Nerve. 2011;44:185–90.

Maher TM, Whyte MKB, Hoyles RK, Parfrey H, Ochiai Y, Mathieson N, et al. Development of a Consensus Statement for the Definition, Diagnosis, and Treatment of Acute Exacerbations of Idiopathic Pulmonary Fibrosis Using the Delphi Technique. Adv Ther. 2015;32:929–43.

Mishra VN, Kalita J, Kesari A, Mitta B, Shankar SK, Misra UK. A clinical and genetic study of spinal muscular atrophy. Electromyogr Clin Neurophysiol. 2004;44:307–12.

Misra UK, Kalita J. Central motor conduction in Hirayama disease. Electroencephalogr Clin Neurophysiol. 1995;97:73–6.

Misra UK, Kalita J, Mishra VN, Kesari A, Mittal B. A clinical, magnetic resonance imaging, and survival motor neuron gene deletion study of Hirayama disease. Arch Neurol. 2005;62:120–3.

Misra UK, Kalita J, Mishra VN, Phadke RV, Hadique A. Effect of neck flexion on F wave, somatosensory evoked potentials, and magnetic resonance imaging in Hirayama disease. J Neurol Neurosurg Psychiatry. 2006;77:695–8.

Peiris JB, Seneviratne KN, Wickremasinghe HR, Gunatilake SB, Gamage R. Non familial juvenile distal spinal muscular atrophy of upper extremity. J Neurol Neurosurg Psychiatry. 1989;52:314–9.

Polo A, Dossi MC, Fiaschi A, Zanette GP, Rizzuto N. Peripheral and segmental spinal abnormalities of median and ulnar somatosensory evoked potentials in Hirayama's disease. J Neurol Neurosurg Psychiatry. 2003;74:627–32.

Sawai S, Misawa S, Kanai K, Isose S, Shibuya K, Noto Y, et al. Altered axonal excitability properties in juvenile muscular atrophy of distal upper extremity (Hirayama disease). Clin Neurophysiol. 2011;122:205–9.

Schlegel U, Jerusalem F, Tackmann W, Cordt A, Tsuda Y. Benign juvenile focal muscular atrophy of upper extremities-a familial case. J Neurol Sci. 1987;80:351–3.

Schroder R, Keller E, Flacke S, Schmidt S, Pohl C, Klockgether T, et al. MRI findings in Hirayama's disease: flexion-induced cervical myelopathy or intrinsic motor neuron disease?. J Neurol. 1999;246:1069–74.

Singh N, Sachdev KK, Susheela AK. Juvenile muscular atrophy localized to arms. Arch Neurol. 1980;37:297–9.

Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G, et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis. 2010;69:631–7.

Sobue I, Saito N, Iida M, Ando K. Juvenile type of distal and segmental muscular atrophy of upper extremities. Ann Neurol. 1978;3:429–32.

Song J, Wang HL, Zheng CJ, Jiang JY. Risk Factors for Surgical Results of Hirayama Disease: A Retrospective Analysis of a Large Cohort. World Neurosurg. 2017;105:69–77.

Tan CT. Juvenile muscular atrophy of distal upper extremities. J Neurol Neurosurg Psychiatry 1985;48:285–6.

Tashiro K, Kikuchi S, Itoyama Y, Tokumaru Y, Sobue G, Mukai E, et al. Nationwide survey of juvenile muscular atrophy of distal upper extremity (Hirayama disease) in Japan. Amyotroph Lateral Scler. 2006;7:38–45.

Tokumaru Y, Hirayama K. Pathomechanism of juvenile muscular atrophy of unilateral upper extremity (Hirayama's disease)–extensibility and asymmetry of the cervical posterior dural wall. Rinsho Shinkeigaku 1994;34:996–1002.
Toma S, Shiozawa Z. Amyotrophic cervical myelopathy in adolescence. J Neurol Neurosurg Psychiatry 1995;58:56–64.
Tynan J, Frangou E, Voll C, Otani R, Harder S. Hirayama disease. Can J Neurol Sci. 2010;37:703–5.
Wang XN, Cui LY, Liu MS, Guan YZ, Li BH, Du H. A clinical neurophysiology study of Hirayama disease. Chin Med J. 2012;125:1115–20.
Willeit J, Kiechl S, Kiechl-Kohlendorfer U, Golaszewski S, Peer S, Poewe W. Juvenile asymmetric segmental spinal muscular atrophy (Hirayama's disease) - three cases without evidence of "flexion myelopathy". Acta Neurol Scand. 2001;104:320–2.
Xu X, Han H, Gao H, Hou C, Fan D, Fu Y, et al. The increased range of cervical flexed motion detected by radiographs in Hirayama disease. Eur J Radiol. 2011;78:82–6.
Yang G, Yang X, Zhang M, Yang Y, Xiao B, Li G, et al. Hirayama Disease in Children From Mainland of China. J Child Neurol. 2014;29:509–13.
Zang L, Fan N, Hai Y, Lu SB, Su QJ, Yang JC, et al. Using the modified Delphi method to establish a new Chinese clinical consensus of the treatments for cervical radiculopathy. Eur Spine J. 2015;24:1116–26.
Zheng C, Zhu D, Lu F, Zhu Y, Ma X, Xia X, et al. A double determination of central motor conduction time in the assessment of Hirayama disease. Clin Neurophysiol. 2017a; 128:2369–74.
Zheng C, Nie C, Lei W, Zhu Y, Zhu D, Wang H, et al. CAN anterior cervical fusion procedures prevent the progression of the natural course of Hirayama disease? An ambispective cohort analysis. Clin Neurophysiol. 2018;129:2341–9.
Zheng C, Zhu D, Lu F, Zhu Y, Ma X, Xia X, et al. Compound Muscle Action Potential Decrement to Repetitive Nerve Stimulation Between Hirayama Disease and Amyotrophic Lateral Sclerosis. J Clin Neurophysiol. 2017b;34:119–25.
Zheng C, Zhu Y, Lu F, Zhu D, Yang S, Ma X, et al. Changes in the soleus H-reflex test and correlations between its results and dynamic magnetic resonance imaging abnormalities in patients with Hirayama disease. Clin Neurophysiol. 2017c;128:2375–81.
Zheng C, Zhu Y, Zhu D, Lu F, Xia X, Jiang J, et al. Motor unit number estimation in the quantitative assessment of severity and progression of motor unit loss in Hirayama disease. Clin Neurophysiol. 2017d;128:1008–14.
Zhou B, Chen L, Fan D, Zhou D. Clinical features of Hirayama disease in mainland China. Amyotroph Lateral Scler. 2010;11:133–9.