Acta Neurologica Belgica (2021) 121:545–553
https://doi.org/10.1007/s13760-019-01253-w

ORIGINAL ARTICLE

Cardiovascular and sudomotor dysfunction in Hirayama disease

Animesh Das[1] · **Sunil Pradhan**[1]

Received: 14 July 2019 / Accepted: 25 November 2019 / Published online: 12 December 2019

Abstract
Hirayama disease is a disease of young males causing atrophy of small muscles of the affected hand and forearm. Localized autonomic dysfunction of the affected upper limb such as cold skin and excessive sweating has been described in some patients. In this study, we looked for local as well as systemic involvement of autonomic nervous system in patients with Hirayama disease. Forty-four patients with a median duration of illness of 3 years were included in the study. Assessment of symptom profile and evaluation of autonomic nervous system were done at the time of enrolment. The mean age at presentation was 21.9 (10–32) years, with a delay in seeking medical attention of around 3 (1–11) years. Localized clinical autonomic dysfunction was present in 39 (88.6%) patients, while objective generalized autonomic dysfunction was present in 33 (75%) patients. Cold skin and excessive sweating showed good correlation with the presence of objective autonomic dysfunction ($P < 0.05$). In three patients, sympathetic skin response (SSR) could not be recorded in one of the four limbs. Compared to controls, the SSR results in patients with Hirayama disease showed increased latency (1.64 ± 0.21 vs. 1.57 ± 0.14, P 0.04) and decreased amplitude in upper limbs (0.65 ± 0.19 vs. 0.86 ± 0.40, P 0.01). Hirayama disease has both localized and systemic dysautonomia. Careful longitudinal evaluation during the progressive phase of the disease may help in diagnosing subtle systemic autonomic dysfunction.

Keywords Sympathetic skin response · Imaging · Hirayama disease · Autonomic nervous system · Dysautonomia

Introduction

Hirayama disease, also known as monomelic amyotrophic (MMA), juvenile muscular atrophy of the distal upper extremity (JMADUE) and juvenile asymmetric segmental spinal muscular atrophy (JASSMA) was first reported by Hirayama et al. in 1959 from Japan [1–4]. He described it as Juvenile muscular atrophy of the unilateral upper extremity [4]. The disease predominantly affects young males sporadically in the late 2nd or early 3rd decades of life. It is characterized by insidious onset unilateral atrophy of hand and forearm muscles in C7/C8/T1 distribution with visible sparing of the brachioradialis, resulting in oblique amyotrophy. Pradhan described bilateral Hirayama disease in 2009 [5]. The pathogenesis of the disease is still unclear, although forward displacement of posterior wall of lower cervical dural canal in flexed neck posture, causing compression and micro-vascular changes of lower cervical cord, has been the most acceptable hypothesis till date [6]. The patients with Hirayama disease generally present with severe visible weakness and wasting in C7/C8/T1 myotomes with occasional EMG evidence of involvement of C6 myotome (brachioradialis) [5]. Autonomic dysfunction in the affected extremities like cold skin, excessive sweating, and hair loss over the dorsum of hand, has also been noted in the literature with severity being more in bilateral disease [1, 5].

Stellate ganglion supplies sympathetic innervation to the upper extremity. It receives pre-ganglionic fibers from T2 to T6 spinal level, while postganglionic fibers are distributed through nerves of brachial plexus. The superior cervical ganglion (T1–T2) gives pupillo-dilator and sudo-motor fibers to the face. Hirayama disease is a disease that has been classically described to involve the C7/C8/T1 myotomes, but sympathetic dysfunction in upper limbs (in the form of excessive sweating) in patients with Hirayama disease suggesting T2–T6 spinal involvement (as preganglionic supply of stellate ganglion which supplies upper limbs is from T2 to T6 spinal segments) shows that it may be a disease with

✉ Animesh Das
animeshdas05@gmail.com

[1] Department of Neurology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, Uttar Pradesh 226014, India

widespread autonomic dysfunction. Therefore, we were interested in studying the autonomic function in Hirayama disease, which has never been studied in great detail.

Methods

The study was conducted in a tertiary care hospital in North India between May 2016 and November 2017. All patients who attended the outpatient clinic of the hospital in the study period and diagnosed with Hirayama disease on the basis of clinical examination, electrophysiological analysis and magnetic resonance imaging of the cervical spine were subjected to different tests for autonomic dysfunction.

A written informed consent was taken from the patient or their guardians (if < 18 years). The patients were considered clinically to be affected with Hirayama disease and included in the study when they had (1) onset of symptoms between their teens and early 20 s, (2) symmetric or asymmetric muscle atrophy in the C7, C8, and T1 myotomal distribution, (3) no sensory loss in the affected upper limbs and no sensory or motor symptom or sign in lower limbs or any other part of the body, (4) relative sparing of brachioradialis (oblique atrophy), (5) tremulousness of fingers seen in outstretched hands (polyminimyoclonus), and (6) initial worsening with cold exposure (cold paresis) [5]. These selection criteria included all the cardinal features of Hirayama disease except unilateral involvement. Due to this single deviation from the original description, the patients with bilateral involvement were included only when they had features of Hirayama disease on electrophysiological investigations and magnetic resonance imaging (MRI) of the cervical spine done in neck flexion.

In case of clinical possibility of a patient being affected with Hirayama disease, nerve conduction studies (NCS) were performed in the electrophysiological lab of the Institute. NCS included motor nerve conduction studies of median, ulnar, radial and peroneal nerves and sensory conduction studies of median, ulnar, radial and sural nerves. F waves in neutral position and cervical flexion were not carried out as NCS studies were done primarily to rule out multifocal motor neuropathy with conduction block (MMNCB). All the upper limb motor nerves were stimulated at wrist, elbow, axilla and erb's point to look for evidence of conduction block (> 50% difference in compound muscle action potential amplitude between proximal and distal stimulation). Lower limb nerves were also stimulated at both proximal (below fibular head) and distal (at the lower tibial border in peroneal) sites. After ruling out MMNCB by NCS, electromyography was performed in bilateral first dorsal interossei (FDI), abductor digiti minimi (ADM), brachioradialis, triceps and vastus medialis. A patient was confirmed to be affected with Hirayama disease only when he had no or minimal decrease in compound motor action potential of median, ulnar and radial nerves with normal NCS in other nerves along with EMG revealing neurogenic changes (fasciculations, fibrillation and neurogenic MUAP) in triceps, FDI, ADM with sparing of brachioradialis and vastus medialis. In case of brachioradialis and vastus medialis also showing neurogenic changes, the case was excluded keeping a possibility of monomelic motor neuron disease. Normative data of nerve conduction studies were followed as given in Preston and Shapiro, 2nd edition.

MRI of the cervical spine was then done in patients with Hirayama disease using 3T scanner (Signa GE medical system, Wisconson USA) in both neutral and flexion position. Reporting of the MRI films was done by an experienced radiologist of the Institute in the following points namely:

(A) In neutral position:
1. Loss of cervical lordosis.
2. Asymmetrical cord flattening.
3. Intramedullary hyperintensity on anterior aspect in cervical region.

(B) In flexion position:
1. Presence of forward movement of the posterior cervical dural wall.
2. Presence of contrast-enhancing crescent-shaped posterior cervical epidural space.
3. Presence of epidural flow voids.
4. Extent of epidural detachment to give a possible diagnosis of Hirayama disease.

Symptoms of cardiovascular autonomic dysfunction like light headedness, dizziness, blurred vision, vertigo, nausea, anxiety, palpitation, clammy feeling on standing, genitourinary dysfunction like impaired early morning erection, impotence, retrograde ejaculation, nocturia, urinary urgency, frequency, retention, incontinence and gastrointestinal dysautonomia like constipation, diarrhea, gastro paresis, early satiety, vomiting, post prandial fullness, fecal urgency and incontinence were noted. The updated version of "Autonomic symptom profile" score with 146 items was used to evaluate patients for autonomic dysfunction [7]. Localized symptoms involving the affected extremity like cold skin, excessive sweating, and hair loss over the dorsum of hands were also noted. Palmar sweating was considered significant when it involved the fingertips in addition to the palm. This is in accordance to International Hyperhydrosis Society criteria of moderate palmar sweating. Sudoscan could not be applied to quantify sweating because of non-availability of the required machine. Patients taking drugs affecting autonomic system like beta-blockers and anticholinergics, alcohol or tobacco in any form were excluded from the study.

Autonomic function tests were done in a quiet room with ambient light and temperature. Spirometric examination

showing normal values of forced vital capacity and forced expiratory volume in the enrolled patients ruled out any involvement of thoracic muscles affecting deep breathing. Heart rate and respiratory rate variability was measured by continuous monitoring on PHILIPS Intellivue MP5 monitor and ratios were calculated after taking printout of ECG strips. The patients were initially made to lie supine on the couch for 20 min before the autonomic nervous system examination was initiated. For cardio vagal function, heart rate variability with deep respiration, expiration: inspiration (*E*:*I*) ratio of the heart rate and 30:15 ratio of R–R interval on standing was analyzed. For sympathetic adrenergic function, blood pressure response to active standing, isometric hand exercise test and mental arithmetic tests were performed. Standard reference values for various parameters were followed for diagnosing autonomic dysfunction [8]. For sympathetic cholinergic sudo-motor function, sympathetic skin response was done in the electrophysiology lab of the Institute. A group of 44 healthy age-matched males also undertook each of the procedures to act as control. These healthy males were only taken as controls after detailed history (for any clinical symptoms), examination (for any signs), nerve conduction studies and supportive EMG for diagnosis of Hirayama disease came negative.

The deep breathing exercise was done according to the standard guidelines to record heart rate variability and *E*:*I* ratio [8]. An average heart rate variability of the six cycles was calculated. The value was considered abnormal if the variability was below the particular age defined cut off which was 14 for 10–29 years, 12 for 30–39 years and 10 for 40–49 years [9]. *E*:*I* ratio of < 1.2 was taken to be abnormal.

For the isometric hand exercise test, the patient was asked to press a mildly inflated BP cuff to maximum strength. He was then asked to maintain the handgrip at 1/3rd of the maximal contraction strength for 3 min. The patient was asked to use the less affected arm for handgrip exercise in case of bilateral disease. Blood pressure measurement was done from the opposite arm every 1 min during the test. If the difference of highest diastolic blood pressure during the test from the average diastolic blood pressure in the subject was less than 15 mm Hg, it was taken as abnormal [8].

Mental arithmetic test and orthostatic test for 30: 15 ratio and orthostatic hypotension respectively were also done according to standard guidelines [8].

The patient was considered to have objective autonomic dysfunction if results of any one of the six parameters (acceleration–deceleration difference, *E*/*I* ratio, 30: 15 ratio, mental arithmetic test, isometric hand exercise test, or orthostatic test) were abnormal.

For the SSR test, the patient was allowed to stay in the electrophysiology lab of the Institute for 15–20 min. The active electrodes were placed on the patient's palms and soles; whereas, reference electrodes were placed on the dorsal aspect of the hand or foot. Low-frequency filter was kept at 0.2 Hz and high-frequency filter was kept at 2000 Hz. Electrical stimulation of median nerve was done by a single square wave pulse of 0.2-ms duration. The stimulus intensity was kept at 30 mA (which normally causes a painful sensation of the median nerve). The absolute value of latency and amplitude values of the response to the first stimulation was considered for quantitative assessments. "No response" was documented when there was no response after 10 consecutive stimuli applied at irregular time intervals. No response in any of the four limbs was taken as an abnormal result.

Ethical clearance

This project was cleared from the Institute's ethical committee (2017-204-IP-100).

Data availability statement

The data will be shared at the request of other qualified investigators for the purpose of replicating procedures and results.

Statistical analysis

The data were analyzed using SPSS software version 20.0, and the results were represented as mean ± standard deviation/range for continuous variables and frequency with percentage for categorical variables. Correlation of each of the parameters of clinical autonomic dysfunction was done with the presence of objective autonomic dysfunction by Pearson's correlation coefficients. Means were compared between two groups with independent *T* tests.

Results

Over a period of 18 months, 44 patients with Hirayama disease were recruited. The baseline characteristics of the patients are given in Table 1.

Most of the patients were males (97%) with only one female in the whole cohort of 44 patients. Bilateral disease was seen in 45.5% cases. The mean age of presentation was 22 years ranging from the beginning of the 2nd decade (10 years) to beginning of the 4th decade (32 years). The mean delay in seeking medical attention from the beginning of the symptoms was 3 years (1–11 years). The percentage of patients with clinically unilateral involvement (54%) in our cohort was almost equal to those with bilateral involvement (45%). Wasting was noted distally in the small muscles of the affected limb (C8, T1 myotome) in 56.8% cases, while both distal and proximal involvement of upper limb (C7, C8, T1 myotome) was seen in remaining 43.1%. Hypoactive

Table 1 Demographic characteristics of the patients

Patient's characteristics	Number (percentage)/mean ± SD (range)
Number of patients	44 (100)
Male	43 (97.7)
Age at presentation (years)	21.9 ± 6.2 (10–32)
Delay in seeking medical attention (years)	3.03 ± 2.1 (1–11)
Presentation	
Unilateral	24 (54.5)
Bilateral	20 (45.5)
Polyminimyoclonus	42 (95.5)
Cold paresis	34 (77.3)
Wasting	
Distal only	25 (56.8)
Distal + proximal	19 (43.1)
Deep tendon reflexes Affected limb	
Hypoactive/Absent	34 (77.3)
Normal	10 (22.7)
Deep tendon reflexes lower limb	
Hyperactive	20 (45.5)
Normal	24 (54.5)
Visible fasciculations in wasted hand	8 (18.2)

reflexes of the affected upper limb were seen in 77.3% cases while brisk lower limb reflexes were noted in 45.5% cases. Polyminimyoclonus was present in 95.5% patients, while visible fasciculations were present in only 18.2% cases (although polyminimyoclonus is also believed to occur due to fasciculations of intrinsic muscles by some authors). More than 3/4th (77.3%) of the patients complained of cold paresis.

Asymmetrical cord flattening in neutral position and contrast-enhanced posterior cervical epidural space in flexed posture was consistently seen in MRI cervical spine of all patients with Hirayama disease (Table 2). Extension of this epidural space to thoracic region up to variable levels was seen in most of the cases (Table 2).

In the NCS studies, when compared to normal values (Table 1), ulnar CMAP (when recorded from abductor digiti minimi) was lower in patients with Hirayama disease (Table 3). Neurogenic MUAPs were present in first dorsal interossei (FDI), triceps and abductor digiti minimi (ADM) of all patients. Spontaneous potentials like fibrillations and fasciculations were present in FDI, ADM and triceps in variable number of patients (Table 4).

None of the patients or evaluated controls had clinical features of generalized cardiovascular, genitourinary or gastrointestinal autonomic dysfunction as assessed by autonomic symptom profile scale. Localized clinical autonomic dysfunction was present in 39 (88.6%) patients. The most common presentations were cold skin and excessive sweating, which were present in about 40–50% of the cases (Table 5).

None of the patients had alteration in baseline heart rate or blood pressure (both systolic and diastolic) from normal values. Objective autonomic evaluation by standard cardiovascular tests revealed autonomic dysfunction in 33(75%) cases. Abnormalities in only one test were found in 21 (63.6%) cases, while more than one test was there in 12 (36%) cases. Among the cardiovascular autonomic tests, acceleration–deceleration difference was found to be the most sensitive to detect abnormalities in patients with Hirayama disease. The frequency of autonomic dysfunction as observed in different tests has been tabulated in Table 6.

Table 2 MRI findings of 44 patients with Hirayama disease

MRI findings	Number (percentage)
Flexion position	
Forward movement of the posterior cervical dural wall on flexion	43 (97.7)
Contrast-enhancing crescent-shaped posterior cervical epidural space	44 (100)
Epidural flow voids	43 (97.7)
Extent of epidural detachment	
Up to lower cervical region	8 (18.2)
Up to lower border of D1[a]	7 (15.9)
Up to lower border of D2	8 (18.2)
Up to lower border of D3	10 (11.4)
More than D3	11 (25)
Neutral position	
Loss of cervical lordosis	40 (90.9)
Cord flattening asymmetrically	44 (100)
Intramedullary hyperintensity on anterior aspect in cervical region	10 (22.7)

[a]*D* Dorsal vertebrae

Table 3 Results of nerve conduction studies

Parameters in affected limb	Latency (Mean ± SD) CMAP (mV), SNAP(μV)	Amplitude in millisec (Mean ± SD)
CMAP[a]		
Median (APB)[b]	3.67 ± 0.26	5.29 ± 0.96
Ulnar (ADM)[c]	2.81 ± 0.42	3.59 ± 0.61
Radial (EIP)[d]	2.57 ± 0.20	2.50 ± 0.94
Common peroneal (EDB)[e]	4.78 ± 0.64	2.77 ± 0.59
SNAP[f]		
Median (digit 2)	2.89 ± 0.38	26.55 ± 4.80
Ulnar (digit 5)	2.75 ± 0.24	28.95 ± 5.05
Radial (snuffbox)	2.55 ± 0.23	24.09 ± 5.65
Sural (posterior ankle)	3.31 ± 0.48	18.98 ± 4.99

[a]*CMAP* Compound muscle action potential
[b]*APB* Abductor pollicis brevis
[c]*ADM* Abductor digiti minimi
[d]*EIP* Extensor indices proprius
[e]*EDB* Extensor digitorum brevis
[f]*SNAP* Sensory nerve action potential

Table 5 Frequency of localized clinical autonomic dysfunction

Parameters	Frequency (percent)	
	Patients (44)	Controls (44)
Cold skin	22 (50)	2 (15.4)
Excessive sweating in the involved limbs	17 (38.6)	1 (7)
Hair loss	2 (4.5)	0

Table 6 Frequency of systemic autonomic dysfunction

Parameters	Frequency (percent)	
	Patients (44)	Controls (44)
Expiration/inspiration ratio	18 (54.5)	0
30/15 ratio	20 (60.6)	0
Isometric hand exercise diastolic BP[a]	14 (42.4)	0
Acceleration–deceleration difference	21 (63.6)	0
Mental arithmetic systolic BP[a]	2 (6)	0
Orthostatic hypotension	0 (0)	0

[a]*BP* Blood pressure

Abnormalities discovered during autonomic function testing were correlated with clinical symptoms of autonomic dysfunction. The degree of correlation is shown in Table 7. Only cold skin and excessive sweating correlated well with objective autonomic dysfunction (P value < 0.05).

We found that most of the patients had both clinical and objective dysautonomia. Furthermore, objective autonomic dysfunction could be additionally identified in three patients who did not have any signs of clinical dysautonomia. Figure 1 shows the overall percentage of patients having clinical or objective autonomic dysfunction.

We also did SSR of all four limbs in patients with Hirayama disease. We found abnormal (absent) SSR in only three patients in our cohort (one in upper limb and two in lower limb). For the comparison of latency and amplitude of SSR between patients and controls, the longest latency and mean amplitude were taken. Though there is low sensitivity to detect dysautonomia by SSR in absolute terms (when absence is taken as abnormal), subtle abnormalities were seen in patients with Hirayama disease. They had decreased amplitude (0.65 ± 0.19 vs 0.86 ± 0.40, P value 0.01) and prolonged latency in upper limbs (1.64 ± 0.21 vs 1.57 ± 0.14, P value 0.04) when compared to normal controls. Figure 2 shows SSR graph from an affected limb of a patient with Hirayama. There has been a controversy in various studies whether to take latency or amplitude measurements of SSR above or below a cut-off point as abnormal. For this reason, we took only absence of SSR as abnormal. The results are shown in Table 8.

Discussion

Autonomic dysfunction was recorded in 75% patients of our study. The most commonly affected parameters were those that were indicative of parasympathetic dysfunction such as *E/I* ratio, acceleration–deceleration difference and 30/15 ratio which were present in more than 50% of the patients. The abnormal findings in these tests, however, appear to be

Table 4 Results of electromyographic examination

Parameters	Number of patients (percentage of total patients)				
	FDI	Triceps	ADM	Brachioradialis	Vastus
Fibrillations	20 (45.5)	12 (27.3)	19 (43.2)	0	0
Fasciculations	15 (34.1)	10 (22.7)	14 (31.8)	0	0
Neurogenic MUAPs[a]	44 (100)	44 (100)	44 (100)	0	0
Normal MUAPs[a]	0	0	0	44 (100)	44 (100)

[a]*MUAP* Motor unit action potential

Table 7 Correlation between clinical dysautonomia with objective autonomic dysfunction

Parameters of clinical autonomic dysfunction	Co-relation with objective autonomic dysfunction (*P* value)
Cold skin	0.001
Excessive sweating	0.001
Hair loss	0.640

generally subclinical as none of these patients manifested clinically with symptoms of generalized parasympathetic dysfunction. The mean latency of SSR in the upper limbs of the patients was also significantly prolonged when compared to controls. This whole sympathetic arc abnormality has already been shown in a previous study by Gourie devi et al. in 2001 [10]. Abnormalities in foot SSR as seen in two of our patients point towards a generalized sympathetic abnormality as the basic physiology of SSR wave generation is difference in skin resistance in response to activation of sweat glands by various exogenous and endogenous stimuli [11]. A little less than half of our patients (42.4%) also had generalized sympathetic dysfunction in the form of diastolic blood pressure abnormality on isometric hand exercise.

Hirayama disease was originally described as a disease causing atrophy of anterior horn cells of C7/C8/T1 spinal

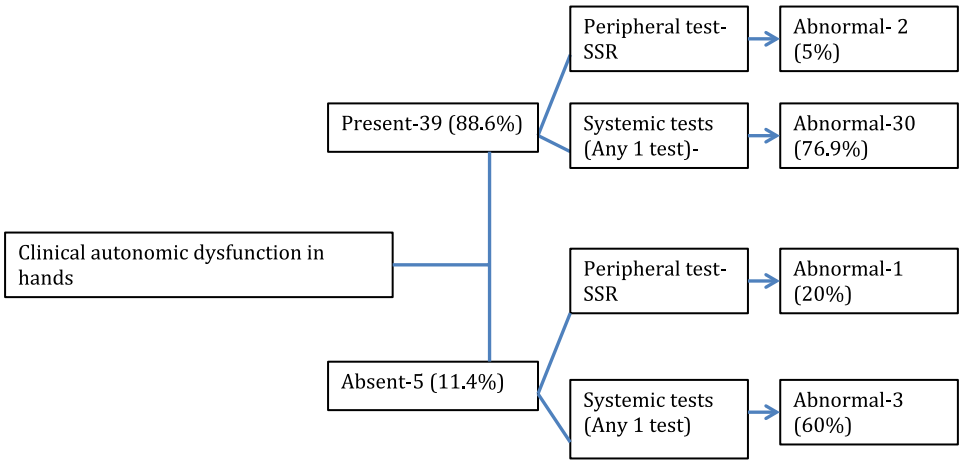

Fig. 1 Percentage of objective autonomic dysfunction in Hirayama patients having clinical dysautonomia

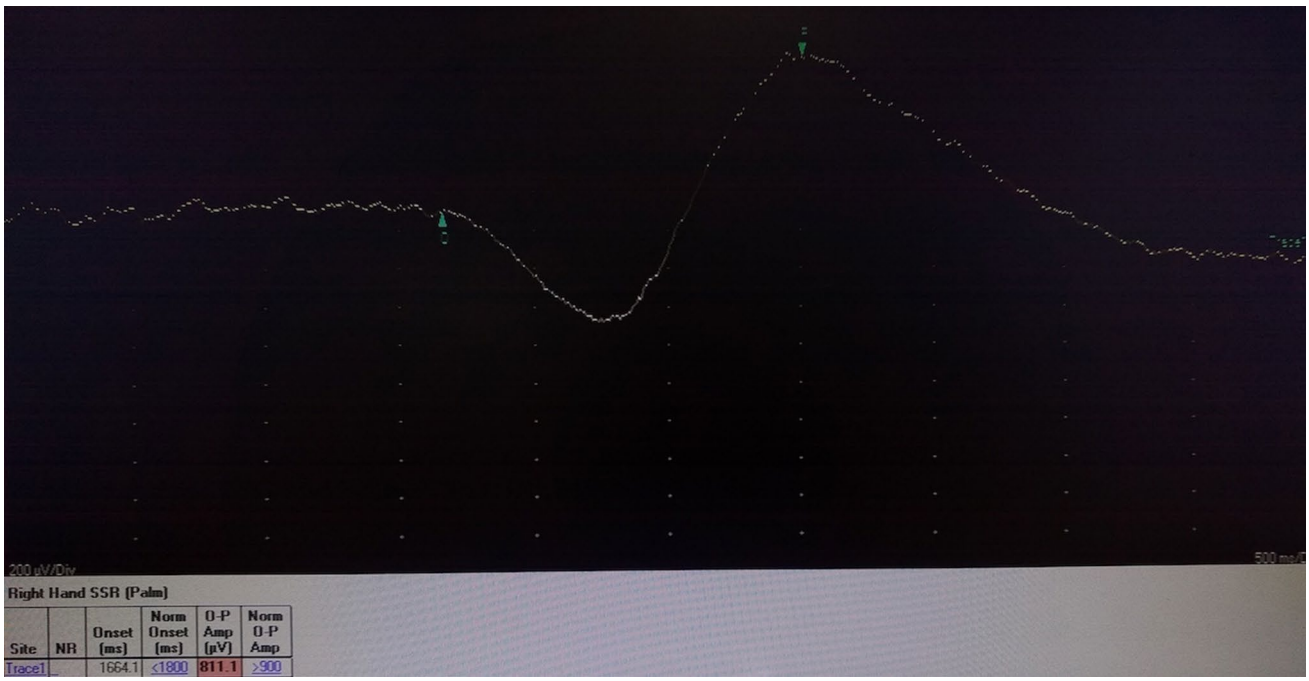

Fig. 2 Sympathetic skin response graph from an affected limb of a patient with Hirayama disease

Table 8 Comparison of latency and amplitude of SSR in patients with Hirayama disease and controls

Parameters of SSR[a]	Controls $N=44$	Patients $N=44$	P value
Longest latency (s)			
UL[b]	1.57 ± 0.14	1.64 ± 0.21	0.04
LL[c]	2.58 ± 0.39	2.43 ± 0.59	0.26
Mean amplitude (mv)			
UL	0.86 ± 0.40	0.65 ± 0.19	0.01
LL	0.48 ± 0.16	0.47 ± 0.28	0.88

[a] *SSR* Sympathetic skin response

[b] *UL* Upper limb

[c] *LL* Lower limb

segments. The upper limb sympathetic supply is known to come from stellate ganglion (T2–T6) through the branches of the brachial plexus. This cannot explain the excessive sweating in Hirayama disease patients as the concerned spinal segments are not involved. Chandrashekhar et al. in 1980 described that intermedio-lateral column in monkeys extended from C8 to L4 spinal segments [12]. As the monkeys' nervous system closely resembles that of human, there is a possibility of some neurons near the non-visible intermedio-lateral columns in the cervical cord of human beings, taking part in maintaining the sympathetic outflow. The involvement of C8, T1 and sometimes T2 spinal segments in Hirayama disease can then explain the excessive sweating in hands of the affected patients. Some animal study on rats have demonstrated a sympathetic projection of neurons lying in the upper cervical cord white matter like lateral cervical nucleus, lateral spinal nucleus and scattered neurons of the lateral funiculus, projecting to the sympathetic preganglionic neurons and intermedio-lateral column (lamina VII) of the upper thoracic cord [13]. Alternately, since in Hirayama disease, epidural crescent has been observed extending up to the upper dorsal spine in some patients, intermediolateral columns of these regions are possibly affected in Hirayama disease and may be contributing to upper limb dysautonomia through the stellate ganglion [14]. These postulates can explain localized upper limb sweating, but fail to explain abnormalities in lower limb SSR, diastolic blood pressure and even the parasympathetic autonomic dysfunction.

Kikuchi et al. postulated that Hirayama disease is due to cervical myelopathy associated with neck flexion [6]. According to him, the posterior dural wall in Hirayama patients shifts anteriorly during flexion of the neck, causing compression of the spinal cord against vertebral body. This causes ischemia, microcirculatory changes and subsequent damage to the anterior horn cells of the cervical spinal cord. The finding of anterior horn cell loss and gliosis with no evidence of ischemia or vascular abnormalities in the pathology finding of one patient by Hirayama et al. argues against this ischemic hypothesis [15]. Pyramidal dysfunction as the cause of occasional lower limb hyperreflexia seen in Hirayama disease has been refuted in electrophysiological studies [16]. In this study, Misra et al. has also concluded against the ischemic theory due to non-involvement of pyramidal tracts, which lie at the border zone of anterior spinal artery. Explaining a disease which presents with predominant lower motor neuron signs in one upper limb and no associated sensory, bladder bowel or pyramidal tract involvement by a possible compressive myelopathic etiology is difficult. Reports of familial Hirayama disease are there in literature, which may point towards a genetic cause [17–20]. Atopy and raised serum IgE levels has also been implicated in the pathogenesis of Hirayama disease in some studies but smaller number of patients (six and one) remains a matter of concern [21, 22]. Willeit et al. have shown in their imaging studies that there was no significant difference in the anterior–posterior diameter of patients and controls [23]. In the light of all these above findings, a hypothesis of some of the authors that Hirayama disease is due to primary degeneration of motor neurons like motor neuron disease (MND) may seem convincing [16]. Now, why this disease stops after progressing focally for few years and motor neuron disease progresses relentlessly remains a matter of research. Recent reports have come up showing that early stage of amyotrophic lateral sclerosis is characterized by vagal withdrawal and sympathetic predominance; while in late stage, sympathetic denervation and vagal predominance follows when intermedio-lateral columns and peripheral sympathetic nerves are destroyed [24–26]. Our findings of decreased *E/I* ratio, 30/15 ratio and acceleration–deceleration difference in the majority of the patients showing parasympathetic under activity, along with increased localized sweating showing sympathetic over activity, can, thus, be explained in Hirayama disease which is a disease more or less similar to MND but with a localized distribution and a benign course. The finding of decreased diastolic pressure on isometric hand exercise and absent SSR in foot may represent a spectrum of autonomic dysfunction along the course of the disease process from sympathetic over activity to sympathetic under activity. Even compressive pathologies like cervical myelopathy can explain some of the autonomic disturbances seen in our patients.

We had shown extensive involvement of both the parasympathetic and sympathetic nervous system parameters in our study. The patients though had only mild localized sympathetic symptoms. Mismatch of this type is well known in advanced cases of MND where only laboratory results were suggestive of hyper functioning of the adrenergic nervous system with the patients having fewer or no symptoms [27]. Estimation of neurotransmitters like adrenaline, noradrenaline, dopamine, acetylcholine and their metabolites can

be done in cases of Hirayama disease to confirm our findings. Effective compensatory mechanisms in the autonomic nervous system and diminished physical activity during the active phase of the disease, which mainly affect the males of 2nd and 3rd decades, may explain why this autonomic dysfunction observed in clinical tests does not manifest clinically on a wider scale.

The limitation of our study is that it was a cross-sectional analysis. Being a disease with generalized autonomic dysfunction, careful observation for further autonomic instability features should be looked for in longitudinal studies, especially during the progressive phase of the disease. A prospective cohort study from the time of presentation to the resolution of the disease with regular follow-up visits may help us to know the natural history of autonomic dysfunction in monomelic amyotrophy. Also, a skin biopsy to look for small fiber neuropathy in the affected patients could have been confirmatory for sympathetic involvement in Hirayama disease.

Conclusion

Hirayama disease has more widespread systemic dysfunction, which can even be present in patients with no clinical dysautonomia.

Acknowledgements The data analysis was performed with the help of Dr. Prabhakar Mishra, Biostatistics department, SGPGI Lucknow. Dr R.V Phadke of Radiology Department, SGPGI Lucknow helped in analysis of the MRI of Hirayama patients. Dr. Azgar of Medical oncology department, AIIMS Delhi provided technical help.

Author contribution AD contributed to the data recording, analysis and final production of the manuscript. SP contributed to the final production of the manuscript.

Funding No sponsorship or funding was received for this study.

Data accessibility Data will be provided if and when asked for by responsible persons.

Complinace with ethical standards

Conflict of interest There is no conflict if interest.

Disclosures AD and SP does not have any disclosure to enclose.

References

1. Gourie-Devi M, Suresh TG, Shankar SK (1984) Monomelic amyotrophy. Arch Neurol 41(4):388–394
2. Biondi A, Dormont D, Weitzner I Jr, Bouche P, Chaine P, Bories JMR (1989) Imaging of the cervical cord in juvenile amyotrophy of distal upper extremity. AJNR Am J Neuroradiol 10(2):263–268
3. Pradhan S, Gupta RK (1997) Magnetic resonance imaging in juvenile asymmetric segmental spinal muscular atrophy. J Neurol Sci 146(2):133–138
4. Hirayama K, Toyokura Y, Tsubaki T (1959) Juvenile muscular atrophy of unilateral upper extremity: a new clinical entity. Psychiatr Neurol Jpn 61:2190–2197
5. Pradhan S (2009) Bilaterally symmetric form of Hirayama disease. Neurology 72(24):2083–2089
6. Kikuchi S, Tashiro K, Kitagawa M, Iwasaki Y, Abe H (1987) A mechanism of juvenile muscular atrophy localized in the hand and forearm (Hirayama's disease) flexion myelopathy with tight dural canal in flexion. Rinsho Shinkeigaku 27(4):412–419
7. Sletten DM, Suarez GA, Low PA, Mandrekar J, Singer W (2012) COMPASS 31: a refined and abbreviated Composite Autonomic Symptom Score. In: Mayo Clinic Proceedings pp: 1196–1201.
8. Zygmunt A, Stanczyk J (2010) Methods of evaluation of autonomic nervous system function. AMS 6(1):11–18
9. Misra UK, Kalita J (2014) Clinical Neurophysiology, 3rd edition. Elsevier, India
10. Gourie-Devi M, Nalini A (2001) Sympathetic skin response in monomelic amyotrophy. Acta Neurol Scand 104:162–166
11. Pierzchała K, Łabuz-Roszak B (2002) Wybrane metody oceny autonomicznego układu nerwowego. Wiadomości Lekarskie 55(5–6):325–331
12. Rao UC, Bijlani V (1980) The intermediolateral gray columns in the spinal cord of Macaca mulatta. J Auton Nerv Syst 2(3):259–267
13. Jansen AS, Loewy AD (1997) Neurons lying in the white matter of the upper cervical spinal cord project to the intermediolateral cell column. Neuroscience 77(3):889–898
14. Raval M, Kumari R, Dung AAD, Guglani B, Gupta N, Gupta R (2010) MRI findings in Hirayama disease. Indian J Radiol Imaging 20(4):245–249
15. Hirayama K, Tomonaga M, Kitano K, Yamada T, Kojima S, Arai K (1987) Focal cervical poliopathy causing juvenile muscular atrophy of distal upper extremity: a pathological study. J Neurol Neurosurg Psychiatry 50:285–290
16. Misra UK, Kalita J (1995) Central motor conduction in Hirayama disease. Electroencephalogr Clin Neurophysiol 97:73–76
17. Pandey S, Jain S (2016) Bilateral familial Hirayama disease in a father and daughter. Ann Indian Acad Neurol 19(2):264–266
18. 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(3):156–160
19. Atchayaram N, Vasudev MK, Goel G (2009) Familial monomelic amyotrophy (Hirayama disease): two brothers with classical flexion induced dynamic changes of the cervical dural sac. Neurol India 57:810–812
20. Robberecht W, Aguirre T, Van den Bosch L, Theys P, Nees H, Cassiman JJ, Matthijs G (1997) Familial juvenile focal amyotrophy of the upper extremity (Hirayama disease) Superoxide dismutase 1 genotype and activity. Arch Neurol 54(1):46–50
21. Kira J, Ochi H (2001) Juvenile muscular atrophy of the distal upper limb (Hirayama disease) associated with atopy. J Neurol Neurosurg Psychiatry 70:798–801
22. Chen TH, Hung CH, Hsieh TJ, Lu SR, Yang SN, Jong YJ (2010) Symmetric atrophy of bilateral distal upper extremities and hyper-IgEaemia in a male adolescent with Hirayama disease. J Child Neurol 25:371–374
23. Willeit J, Kiechl S, Kiechl-Kohlendorfer U, Golaszewski S, Peer S, Poewe W (2001) Juvenile asymmetric segmental spinal muscular atrophy (Hirayama's disease): three cases without evidence of "flexion myelopathy". Acta Neurol Scand 104(5):320–322
24. Pavlovic S, Stevic Z, Milovanovic B, Milicic B, Rakocevic-Stojanovic V, Lavrnic D, Apostolski S (2010) Impairment of cardiac

autonomic control in patients with amyotrophic lateral sclerosis. Amyotroph Lateral Scler 11:272–276
25. Shimizu T, Kawata A, Kato S, Hayashi M, Takamoto K, Hayashi H, Hirai S, Yamaguchi S, Komori T, Oda M (2000) Autonomic failure in ALS with a novel SOD1 gene mutation. Neurology 54:1534–1537
26. Asai H, Hirano M, Udaka F, Shimada K, Oda M, Kubori T, Nishinaka K, Tsujimura T, Izumi Y, Konishi N, Matsumoto S, Kameyama M, Ueno S (2007) Sympathetic disturbances increase risk of sudden cardiac arrest in sporadic ALS. J Neurol Sci 254:78–83
27. Sato K, Namba R, Hayabara T, Kashihara K, Morimoto K (1995) Autonomic nervous disorder in motor neuron disease: a study of advanced stage patients. Intern Med 34(10):972–975