

SHORT REPORT

HyperIgEaemia in patients with juvenile muscular atrophy of the distal upper extremity (Hirayama disease)

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Background: Juvenile muscular atrophy of the distal upper extremity (Hirayama disease) is characterised by anterior horn cell loss in the lower cervical cord, presumably caused by anterior displacement of the dural sac during neck flexion. A recent report suggests that atopy and IgE may contribute to anterior horn damage.

Objective: To investigate whether IgE is a contributing factor in Hirayama disease.

Methods: Serum total IgE and allergen specific IgE were examined in 20 consecutive patients, and their correlations with clinical profiles investigated.

Results: Past or present history of allergy/atopy was found in only four patients (20%), but serum IgE was raised in 14 (70%). Patients with hyperIgEaemia had more severe clinical disabilities than those without ($p=0.01$). In patients whose history of Hirayama disease was less than five years, serum total IgE was higher than in those with the disease for five years or more ($p=0.05$).

Conclusions: The results suggest that hyperIgEaemia is often associated with Hirayama disease and can facilitate its pathophysiology, particularly in the early phases of the disease. HyperIgEaemia does not appear to involve the anterior horn cells primarily.

Juvenile muscular atrophy of the distal upper extremity (Hirayama disease) is characterised by muscular weakness and wasting of the distal upper extremity, predominantly in young men,^{1–3} and is followed by spontaneous arrest within several years.⁴ Upper extremity involvement is primarily unilateral. The pathophysiology of Hirayama disease has not yet been clarified, but neuroimaging studies suggest that the disorder is a type of flexion myelopathy—abnormal forward displacement of the cervical dural sac during neck flexion results in compression of the lower cervical cord.^{2–3} Necropsy findings show shrinkage and loss of the anterior horn cells of the cervical cord, possibly caused by circulatory insufficiency in the spinal cord.⁵

Recently, Kira and Ochi reported five patients with Hirayama disease in association with atopy,⁶ and raised the possibility that hyperIgEaemia contributes to anterior horn damage. As the frequency of hyperIgEaemia in patients with Hirayama disease and its action on the pathophysiology are currently unknown, we undertook the present study to determine the frequency of hyperIgEaemia and its correlation with the clinical and electrophysiological profiles of patients with Hirayama disease.

METHODS

We examined 20 consecutive patients with Hirayama disease (19 men, one woman) seen at Chiba University Hospital between 1992 and 2001. Their ages ranged from 17 to 32

years (mean (SD), 20.6 (4.2) years). The age of onset of the disease ranged from 12 to 19 years (15.8 (2.2) years), and the disease duration from 1 to 20 years (4.8 (5.2) years). All patients had typical clinical features of Hirayama disease.^{2–3} In order to establish the diagnosis we required confirmation of forward displacement of the cervical dural sac during neck flexion on magnetic resonance imaging (MRI) or computed tomographic (CT) myelography (fig 1).

Hirayama disease usually involves one upper limb, and this was the case in all 20 of our patients. The clinical severity of the disease was evaluated using the following grading⁴: *grade 1* ($n=8$), grip strength of the affected hand more than 50% of the non-affected hand; *grade 2* ($n=6$), grip strength of the affected hand 30–50% of the non-affected hand; *grade 3* ($n=6$), grip strength of the affected hand less than 30% of the non-affected hand.

We asked patients and their family members whether they had a past, present, or family history of allergy/atopy, such as atopic dermatitis, bronchial asthma, allergic rhinitis, pollinosis, or diet allergy. Serum total IgE and allergen specific IgE concentrations (radioallergosorbent test: RAST) for mites (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), house dusts, cedar pollen, and soybean were measured. A serum total IgE level of greater than 170 IU/ml was considered abnormal.⁷ RAST values of over 0.34 allergen unit (AU)/ml were considered abnormally high; the values were classified as follows: *class 1*, 0.35 to 0.69; *class 2*, 0.70 to 3.49; *class 3*, 3.50 to 17.49; *class 4*, 17.50 to 49.99; *class 5*, 50.00 to 99.99; and *class 6*, over 100.00.

Electromyography was carried out in 16 patients, and active denervation was considered to be present when fibrillation potentials or positive sharp waves were found in the first interosseous muscle or flexor carpi ulnaris muscle on the affected side. Eighteen patients underwent motor nerve conduction studies on the ulnar nerve of the affected side.

For statistical analyses, differences in medians were tested by the Mann–Whitney U test, and differences in proportions by Fisher's exact test.

RESULTS

In our 20 patients, at least one kind of past or present history of allergy/atopy was present in four (20%): atopic dermatitis in three (15%), allergic rhinitis in one (5%), and pollinosis in one (5%). No patient had a history of bronchial asthma or diet allergy. A familial history of at least one kind of allergy/atopy was found in seven patients (35%): atopic dermatitis in three (15%), allergic rhinitis in four (20%), bronchial asthma in four (5%), and diet allergy in four (5%).

HyperIgEaemia was present in 14 of the 20 patients (70%) (mean 655 IU/ml; range 180 to 4100 IU/ml). The values of at least one kind of RAST were abnormally high in 16 patients (80%): house dusts in 13 (65%), mites in 13 (65%), cedar pollen in 14 (70%), and soybean in three (15%). Table 1 compares the clinical, immunological, and electrophysiological profiles of patients with hyperIgEaemia and

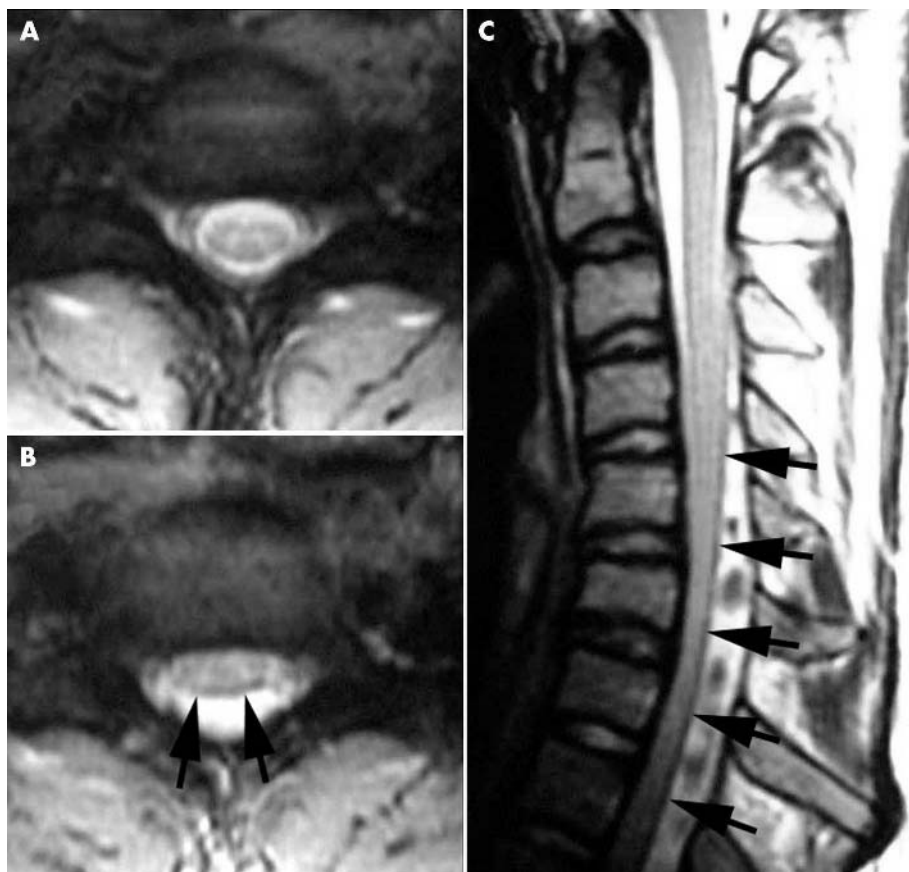


Figure 1 T2 weighted magnetic resonance images of the cervical region in a patient with typical features of Hirayama disease. The black arrow indicates the posterior wall of the dural sac. An axial image at the C6 vertebral level at neutral cervical position shows no apparent abnormality of the cervical cord or dural sac (A). During neck flexion, axial (B) and sagittal (C) images show abnormal forward displacement of the dural sac at the lower cervical level with compression of the spinal cord (arrows).

those without. Age, age of onset, male to female ratio, and disease duration did not differ significantly between the two subgroups. With respect to the clinical grade, hyperIgEaemia was found in four of eight grade 1 patients (50%), in three of six grade 2 patients (50%), and in five of six grade 3 patients (83%). Clinical severity was significantly greater in patients with hyperIgEaemia (mean clinical grade, 2.0) than in those without (mean clinical grade, 1.0) ($p = 0.01$); RAST values for mites and house dusts were also higher in patients with hyperIgEaemia than in those without. Patients with hyperIgEaemia tended to have lower amplitudes of ulnar compound muscle action potentials and more frequent active denervation potentials, but the differences were not statistically significant. The lack of statistical difference in the electrophysiological variables might reflect the small number of patients and muscles examined. Disease duration correlated with the serum IgE concentrations; the patients with Hirayama disease for less than five years had a higher serum IgE than those with the disease for five years or more ($917 (1286) v 262 (160) \text{ IU/ml}$; $p = 0.05$).

DISCUSSION

Our study confirms previous findings⁶ that patients with Hirayama disease often suffer from hyperIgEaemia (70% in this study), and furthermore show that patients with hyperIgEaemia tend to have more severe disabilities than those without. Moreover, serum IgE concentrations are higher in patients with a disease duration less than five years than in those with a duration of five years or more.

These findings suggest that IgE may be a facilitating factor in the severity and activity of the disease, especially in its early phases. However, a third of our patients showed no evidence of atopy and had normal serum IgE levels.

Recent studies have shown that the prevalence of atopic dermatitis,⁸ allergic or seasonal rhinitis,⁹ and pollinosis^{9, 10} in Japan is 11–24%, 29–36%, and 11–23%, respectively. Comparing these data, the frequency of a history of atopy/allergy was considered low in our patients with Hirayama disease, but an asymptomatic increase in serum total IgE (70%) and RAST (80%) was very common.

Although various reports have stated that MRI during neck flexion does not show dural sac displacement in some patients with Hirayama disease,^{11, 12} our present study included a uniform group of patients, in all of whom abnormal forward displacement of the cervical dural sac was confirmed. In such patients, dural sac displacement during neck flexion and the resulting cord compression are assumed to contribute to anterior horn cell damage.

The relation between dural sac displacement and hyperIgEaemia in Hirayama disease is unknown. The dural sac is normally tightly connected to the spinal canal wall, and its abnormal displacement is probably caused by mechanical or other unknown factors. Eosinophils are known to secrete matrix metalloproteinases, especially matrix metalloproteinase-9,^{13, 14} and we recently reported that cervical intervertebral disc degeneration is common in patients with atopy and hyperIgEaemia,¹⁵ suggesting a possible relation between atopy and an abnormality of connective

Table 1 Clinical and laboratory profiles of patients with Hirayama disease

	Serum IgE		p Value
	Normal (n = 6)	Raised (n = 14)	
Age (years)	19.2 (1.2)	21.1 (4.9)	NS
Age at onset (years)	15.2 (2.0)	16.0 (2.3)	NS
Male to female ratio	5:1	14:0	
Disease duration (years)	4.0 (2.4)	5.1 (6.0)	NS
Clinical grade* (median (range))	1.0 (1.0–2.0)	2.0 (1.0–3.0)	0.01
History of atopy/allergy	17%	21%	NS
Serum IgE level (IU/ml)	87 (43)	899 (1165)	0.01
Radioallergosorbent test			
Mite	1.0 (1.2)	2.6 (2.2)	0.03
House dust	0.8 (1.3)	2.7 (2.2)	0.02
Cedar pollen	2.7 (2.2)	2.4 (2.1)	NS
Soybean	0	0.4 (0.9)	
Electrophysiology			
Ulnar CMAP (mV)	3.3 (2.0)	2.8 (1.4)	NS
Active denervation on EMG	2 of 4	9 of 13	NS

Values are mean (SD) unless indicated.

*See text.

CMAP, compound muscle action potential.

tissues. Atopy or hyperIgEaemia may affect collagen or other connective tissue components of the dural sac in patients with Hirayama disease. It is possible that such involvement of the connective tissues results in impaired dural development. Hirayama disease predominantly affects young male adolescents in their mid-teens,^{2,3} the age at which their height increases most rapidly. Abnormal dural sac displacement in patients with Hirayama disease may be related to connective tissue abnormalities during this period of rapid growth.

Further studies are required to determine the mechanisms of action of IgE on loss of anterior horn cells in Hirayama disease. Although a previous report raised the possibility that IgE directly causes spinal anterior horn damage through circulatory insufficiency resulting from platelet activation and arterial spasm,⁶ we believe that this is unlikely, because a third of our patients with Hirayama disease had no evidence of atopy or hyperIgEaemia during the progressive phase of the disease, though they did show abnormal dural sac displacement.

We speculate that indirect effects on the dural sac by IgE as described above facilitate the mechanical pathophysiology in Hirayama disease. The present study shows that the serum total IgE level is higher in patients who were in their early progressive phase, and is associated with more severe clinical disability; these patients tended to have more prominent electrophysiological abnormalities. Suppression of IgE may be a treatment option, especially in the early phases of the disease.

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REFERENCES

- Hirayama K, Toyokura Y, Tsubaki T. Juvenile muscular atrophy of unilateral upper extremity: a new clinical entity. *Psychiatr Neurol Jpn* 1959;**61**:2190–8 [abstract in English].
- Hirayama K. Juvenile muscular atrophy of distal upper extremity (Hirayama disease). *Intern Med* 2000;**39**:283–90.
- Hirayama K, Tokumaru Y. Cervical dural sac and spinal cord in juvenile muscular atrophy of distal upper extremity. *Neurology* 2000;**54**:1922–6.
- Tokumaru Y, Hirayama K. Cervical collar therapy for juvenile muscular atrophy of distal upper extremity (Hirayama disease). *Int Med* 2000;**39**:283–90.
- Hirayama K, Tomonaga M, Kitano K, et al. Focal cervical poliopathy causing juvenile muscular atrophy of distal upper extremity: a pathological study. *J Neurol Neurosurg Psychiatry* 1987;**50**:285–90.
- Kira J, Ochi H. Juvenile muscular atrophy of the distal upper limb (Hirayama disease) associated atopy. *J Neurol Neurosurg Psychiatry* 2001;**70**:798–801.
- Shimazu S, Enomoto T. Serum IgE levels in healthy children. *Arerugi no Ryoiki* 1995;**2**:62–7 [in Japanese].
- Sugiura H, Umemoto N, Deguchi H, et al. Prevalence of child food and adolescent atopic dermatitis in a Japanese population: comparison with the disease frequency examined 20 years ago. *Acta Derm Venereol* 1998;**78**:293–4.
- Sakurai Y, Nakamura K, Teruya K, et al. Prevalence and risk factors of allergic rhinitis and cedar pollinosis among Japanese men. *Prev Med* 1998;**27**:617–22.
- Ozasa K, Deijima K, Takenaka H. Prevalence of Japanese cedar pollinosis among schoolchildren in Japan. *Int Arch Allergy* 2002;**128**:165–7.
- Schröder R, Keller E, Flacke S, et al. MRI findings in Hirayama's disease: flexion-induced cervical myelopathy or intrinsic motor neuron disease? *J Neurol* 1999;**246**:1069–74.
- Willeit J, Kiechl S, Kiechl-Kohlendorfer U, et al. Juvenile asymmetric segmental spinal muscular atrophy (Hirayama's disease). Three cases without evidence of "flexion myelopathy". *Acta Neurol Scand* 2001;**104**:320–2.
- Fujisawa T, Kato Y, Terada A, et al. Matrix metalloproteinase-9 in peripheral blood eosinophils. *Int Arch Allergy Immunol* 1999;**120**(suppl 1):65–9.
- Schwingshackl A, Duszyn M, Brown N, et al. Human eosinophils release matrix metalloproteinase-9 on stimulation with TNF- α . *J Allergy Clin Immunol* 1999;**104**:983–9.
- Ito S, Hattori T, Fukutake T, et al. Is atopic dermatitis a risk factor for intervertebral disc degeneration? A preliminary clinical and MRI study. *J Neurol Sci* 2003;**206**:39–42.