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

S Ito, S Kuwabara, T Fukutake, Y Tokumaru, T Hattori

**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.

**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 three (15%), bronchial asthma in three (15%), and diet allergy in three (15%). Table 1 compares the clinical, immunological, and electrophysiological profiles of patients with hyperIgEaemia and

**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.

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 grading (1–6): grade 1 (n = 1), mild; grade 2 (n = 6), grip strength of the affected hand more than 50% of the non-affected hand; grade 3 (n = 6), grip strength of the affected hand 30–50% of the non-affected hand; grade 4 (n = 5), grade 5 (n = 3), and grade 6 (n = 1).

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.
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 ampli-
tudes 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) vs. 262 (160) IU/ml; \( p = 0.05 \)).

**DISCUSSION**

Our study confirms previous findings\(^5\) 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,\(^4\) allergic or seasonal rhinitis,\(^4\) and pollinosis\(^10\) 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,\(^9,11,12\) and we recently reported that
cervical intervertebral disc degeneration is common in pati-
ents with atopy and hyperIgEaemia,\(^13\) suggesting a possible
relation between atopy and an abnormality of connective
tissues. Atopy or hyper-IgEaemia 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, 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, we believe that this is unlikely, because a third of our patients with Hirayama disease had no evidence of atopy or hyper-IgEaemia 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.

ACKNOWLEDGEMENTS

We would like to express our gratitude to Dr Keizo Hirayama for helpful comments on the manuscript.

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Competing interests: none declared

Table 1 Clinical and laboratory profiles of patients with Hirayama disease

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<tr>
<th></th>
<th>Serum IgE</th>
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<tr>
<td></td>
<td>Normal</td>
<td>Raised</td>
<td>p Value</td>
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<tr>
<td>Age (years)</td>
<td>19.2 (2.1)</td>
<td>21.1 (4.9)</td>
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<td>Age at onset (years)</td>
<td>15.2 (2.0)</td>
<td>16.0 (2.3)</td>
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<td>Male to female ratio</td>
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<td>14.0</td>
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<td>Disease duration (years)</td>
<td>4.0 (2.4)</td>
<td>5.1 (6.0)</td>
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<td>Clinical grade* (median (range))</td>
<td>1.0 (1.0–2.0)</td>
<td>2.0 (1.0–3.0)</td>
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<td>History of atopy/allergy</td>
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<td>21%</td>
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<td>Serum IgE level (IU/ml)</td>
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<td>899 (1165)</td>
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<td>Radioallergosorbent test</td>
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<td>Mite</td>
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<td>House dust</td>
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<td>Cedar pollen</td>
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<td>Soybean</td>
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<td>Ulnar CMAP (mV)</td>
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<td>Active denervation on EMG</td>
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Values are mean (SD) unless indicated.

*See text.

CMAP, compound muscle action potential.

REFERENCES


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Received 4 November 2003
In revised form 15 February 2004
Accepted 25 April 2004