Juvenile Muscular Atrophy of Distal Upper Extremity (Hirayama Disease)

Keizo Hirayama

Abstract

This disease is characterized by initially progressive muscular weakness and wasting of the distal upper limb(s) in young people predominantly in men, followed by a spontaneous arrest within several years. This disease has been thought to be separate from motor neuron diseases, yet some authors still consider the illness a variant of motor neuron disease. However, the pathological evidence of ischemic changes in the lower cervical anterior horn should facilitate differentiation of the disorder from degenerative motor neuron disease. Recent radiological investigations proved compressive flattening of the lower cervical cord due to forward displacement of the cervical dural sac and spinal cord induced by neck flexion. These findings suggest that sustained or repeated neck flexion may cause ischemic changes in the cervical anterior horn. Application of a cervical collar to minimize neck flexion prevents progressive muscular weakness in an early stage of the disease.

Clinical Features

The clinical features are summarized based on both old and new case series (1–3, 5, 6). This disease develops in young people in their teens and early twenties (Fig. 1), predominantly in men (male to female ratio = 20:1). Familial occurrence is quite rare; six pairs have been reported in over 300 case reports. The onset is insidious with muscular weakness and wasting in the hand and forearm sparing the brachioradialis muscle (Fig. 2). The border of muscular atrophy runs obliquely over both volar and dorsal surfaces of the forearm (oblique amyotrophy). The amyotrophy is unilateral in most patients, asymmetrically bilateral in some, and rarely symmetric. Weakness develops in both extensor and flexor muscles of the fingers and wrist; the finger extensors and wrist flexors are usually predominantly involved. Most patients (97%) report that weakness of fingers easily worsens on exposure to cold environment (cold paresis). There are no fasciculations at rest, but fascicular twitching of the forearm muscles accompanies tremulous movement of the fingers on weak finger extension (contraction fasciculation). Although subjective and objective sensory disturbances are usually absent, a few patients show slight hypoesthesia in a localized area of the hand. Muscle stretch reflexes of the arms and legs are within the normal range. There is no cranial nerve involvement, no pyramidal signs, and no urinary disturbances. The initial slowly progressive course is followed by a spontaneous arrest within several years after onset, within 5 years in 73% of patients.

Hirayama and associates (1–3) pointed out that the clinical features of the disease had some resemblance to "téphromalacie antérieure" reported by Marie and Foix in 1912 (7), which shows muscular wasting restricted in the distal upper limbs in middle aged or elderly people, pathologically due to softening of the anterior horn in the lower cervical cord. Although the mechanisms of cervical cord damage may be different, the clinical resemblance suggested pathology of the lower cervical cord in

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figure 1. Distribution of age at onset of the disease. There is a peak at 16 years. (Department of Neurology, School of Medicine, Chiba University from 1982 to 1992)

Figure 2. Muscular atrophy of the left arm. Localized atrophy of the hand and forearm spares the brachioradialis muscle, and shows oblique amyotrophy.

juvenile muscular atrophy of distal upper extremity.

Laboratory Findings

Muscle biopsy of the atrophic muscles shows typical neurogenic changes with clusters of small angular fibers and large type groupings indicative of reinnervation (8). Cerebrospinal fluid shows normal cellular content with or without a slight increase in protein (40–60 mg/dl; normal <40 mg/dl). Pressure curve of the Queckenstedt test shows a slightly slow and insufficient rise and fall in the neutral neck position, which is aggravated when the neck is flexed (9).

There are several electrophysiological investigations. Electromyography shows acute and chronic denervation in the atrophied muscles. The homonymous muscles of the unaffected side also show denervation in about 90% of patients with unilateral amyotrophy. Non-atrophic muscles on the affected side sometimes show denervation, in 50% of triceps brachii, and in less than 25% of brachioradialis, biceps brachii, and deltoid muscles (10, 11). Single fiber electromyography shows increased fiber density and jitter in a progressive stage. The fiber density further increases but jitter decreases in a late, non-progressive stage, indicating maturation of reinnervation (12). Motor nerve conduction velocities are normal, except for minimal slowing in ulnar nerve conduction (13). Amplitude of compound muscle action potentials is reduced in the atrophied muscles.

F-wave shows a minimal increase in latency, low persistency (13), and a singular, high-amplitude waveform suggesting denervation/reinnervation (14). F-wave persistency decreases when the neck is flexed in a progressive phase of the disease, which could be an indicator to stop a cervical collar therapy, as will be described later (13, 15). Somatosensory evoked potentials may show abnormal conduction through the spinal cord (16). Motor evoked potentials after transcranial magnetic stimulation shows an increased latency and decreased amplitude, which is temporally aggravated by neck flexion (15, 17). Several parameters are worsened by neck flexion, suggesting a pathogenetic role of neck flexion in this disease, and giving a rational base for cervical collar therapy.

Cold paresis is also studied electrophysiologically. When the cold paresis is induced, compound muscle action potentials after high-frequency repetitive nerve stimulation show delayed latencies and decreased amplitudes, suggesting impaired conduction through muscle membrane (18). Neuroradiological findings will be described later.

Neuropathology

Opportunity for autopsy is quite rare because of the excellent prognosis of the disease compared to the classical motor neuron diseases. The first autopsy case was obtained in 1982 (19, 20), when a quarter of century had passed since the first clinical case report. The patient was a man who suffered from lung cancer for 3 months and died at the age of 38. He had disease onset at the age of 15, and had muscular weakness and wasting in the distal upper limbs predominantly on the left for 23 years. The spinal cord showed macroscopically evident antero-posterior flattening at the lower cervical segments. Microscopically, the antero-posterior diameter of the lower cervical anterior horns of both sides was reduced, most severely at C7 and C8 predominantly on the left. The anterior horn lesion was characterized by a decreased number of both large and small neurons, mild astrogliosis, and central necrosis without cavity formation (Fig. 3). The surviving neurons showed various stages of degenerative changes. The white matter, posterior horns, and the intra- and extramedullary vessels were normal. There were no metastatic or spondylotic changes in
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Figure 3. Myelin stain of transverse section of the spinal cord. Anterior horns on both sides shrink anteroposteriorly, most severely at C7 and C8 predominantly on the left, the side of predominant muscular atrophy. Kluver-Barrera stain.

the cervical vertebrae and cord. Losses of not only large but also small neurons, a weak gliosis, and central necrosis in the anterior horns were quite unlikely in degenerative motor neuron disease. We concluded that those changes are ischemic as reported preliminarily in 1985 (19) and published in 1987 (20).

Araki et al (21) from Japan reported the second autopsy case. The patient was a 76-year-old man who had a disease onset at age 24, but was complicated by cervical spondylosis in his later life. The neuropathological findings were comparable to those of the first case except for the rostral extension of the lesion up to C2 probably due to concomitant cervical spondylosis.

In conclusion, the pathological findings strongly suggested that the disease is an ischemic cervical myelopathy localized in the lower cervical cord, and excluded the possibility of motor neuron disease. Further detailed information on the neuropathological findings is published elsewhere (22).

Neuroradiological Investigations

Neuroradiological techniques up to 1970’s did not disclose any radiological abnormalities of the disease. Pathological evidence for a cervical myelopathic origin of the disease prompted radiological investigations, and advancement of the techniques enabled investigation of the contents of the spinal canal after 1980. Some Japanese authors reported dynamic changes in the spinal canal induced by neck flexion in patients with the disease, and named anterior shift of the dural sac (23), over-stretch of the cord (24, 25), tight dural canal in flexion (26), or disproportionate shortening of the dorsal roots (27), based on their hypothetical mechanisms of dynamic changes in the spinal canal.

We examined the specificity and significance of those changes in 73 consecutive patients and in 20 controls using myelography and CT-myelography since 1981, and magnetic resonance imaging (MRI) which became available after 1986 (28). We employed an order-made pelvic wedge to obtain a fully-flexed position of the neck on the CT or MRI table. Insufficient flexion of the neck may account for the absence of the dynamic changes in patients with this disorder, as seen in several case reports. Only full flexion of the neck results in the dynamic changes.

In the neutral neck position, mild to moderate atrophy of the lower cervical cord was detected in 65% of patients by myelography, in 88% by CT-myelography, and in 49% by MRI. The dural sac is located normally in the neutral neck position. Full flexion of the neck produced remarkable changes in the position and shape of the dural sac and spinal cord. The dural sac was displaced forward and tightened, accompanying postero-anterior flattening of the lower cervical cord (Figs. 4 and 5). These findings were seen in 88% of patients by myelography, in 94% by CT-myelography, and 87% by MRI. The cord flattening was asymmetrical; the more flattened side corresponded to the more atrophied limb (Fig. 5).

We calculated the decrement ratio of the antero-posterior (AP) diameter of the dural sac on myelogram and CT-myelogram by the equation: \((Dn-Df)/Dn\), where \(Dn\) is AP diameter of the dural sac at neutral neck position, and \(Df\) is the diameter on full neck flexion. The decrement ratio was inversely correlated with the duration of illness (Fig. 6). Patients who had a disease duration more than 20 years had normal decrement ratio of the dural AP diameter. Younger patients <30 years old who had a disease duration <10 years had a greater decrement ratio than the age-matched controls (\(p<0.001\)), and than the older patients >30 years old who had a disease duration >17 years (\(p<0.001\)).

These statistical findings indicated that the forward displacement of the dural sac and tightening of the spinal cord on neck flexion are specific to young patients having a short duration of illness and a progressive stage of the disease. The dural displacement then gradually decreases and finally disappears with increasing age and disease duration. This chronological course is well comparable to the clinical course of the disease, which is initially progressive for several years, then followed by a spontaneous arrest. The absence of forward displacement of the dural sac and cord compression in elderly patients whose disease had arrested suggested that the dynamic compression
Figure 4. Lateral view of myelogram in a neutral (A) and a flexed (B) position of the neck. (A) The position and diameter of the cervical dural sac are normal in a neutral neck position. (B) On neck flexion, the dural sac shifts forward with tightening in the antero-posterior direction at the C5-7 vertebral levels.

Figure 5. CT myelogram in a neutral (A) and a flexed (B) position of the neck. From the top to the bottom, transverse sections of C3, C4, C5, C6, and C7 vertebral levels are arranged. (A) The position of the dural sac is normal. There is mild antero-posterior flattening of the spinal cord at the C6 vertebral level. (B) Full neck flexion induces forward displacement of the dural sac and remarkable flattening of the spinal cord at the C5–7 vertebral levels.

Figure 6. Correlation between the decrement ratio of the dural A-P diameter ((Dn-Df)/Dn) and disease duration (years) in 60 patients. The decrement ratio is inversely correlated to the disease duration.

Reports from Other Countries

Pilgaard made the first case report outside Japan from Denmark as early as in 1968 (35). However, thereafter, there were fewer case reports from other countries than from Japan. All of the case reports outside Japan are listed in Table 1 (35–58). Recently, reports on radiological (46, 48–50, 56, 58) and electrophysiological (48, 50–54) findings of the disease are ac-

has a pathogenetical significance.

In a fully-flexed position of the neck, posterior epidural space that was low-density in CT-myelography appeared as a high signal on T1- and T2- weighted images of MRI (Fig. 7), suggesting circulatory changes in the spinal canal during neck flexion. These findings seem to represent passive dilatation of the posterior internal vertebral venous plexus due to forward displacement of the cervical dural sac (23, 29, 30). Other authors attribute the findings to congestion of the venous plexus (31, 32), abnormal drainage in the vertebral venous plexus (33), or epidural vascular malformation (34). Whatever the mechanisms, the epidural high signal may not be the primary cause of the disease because it transiently appears only on neck flexion. In addition, cinematographic MRI showed signal voids in the epidural high signal, which pulsed synchronously with cardiac pulsation (23).
cumulating. Some authors suspect the disease to be a variant of motor neuron disease (37, 39, 41, 53, 57, 58), which had been discussed in Japan, but was disregarded after the first autopsy described above. Some authors (42, 46, 49, 50, 53, 57) include the disease as “monomelic amyotrophy” that means muscular wasting limited in any one of upper or lower limbs and implies focal motor neuron degeneration. We had a similar argument of “glove and stocking type amyotrophy” in 1960’s (59). Recently, however, no one includes the disease as “glove and stocking type amyotrophy” in Japan. Juvenile muscular atrophy of distal upper extremity should be separated from “monomelic amyotrophy” until the common pathogenesis of these disorders is established.

**Possible Mechanisms and Therapy**

The pathological findings and the results of radiological studies suggest the following pathogenetic mechanism of this disease. Repeated or sustained neck flexion may cause an anterior shift of the cervical dural sac which is then compressed against the posterior margin of the vertebral body. The lower cervical cord at the C6 vertebral level, i.e. at the C7 and C8 cord segments, is squeezed postero-anteriortly by the tightened dural sac. The compressed cervical cord at these segments has an increased intramedullary pressure that results in microcirculatory disturbances in the anterior horn, the most vulnerable structure to ischemia in the spinal cord (60). Provided that this mechanism of an increased intramedullary pressure is operating, maintaining the flexed neck position during writing at a desk or playing musical instruments may worsen the disease. We asked 63 patients about these activities, and four of them had appearance or worsening of the muscular weakness while playing guitar or piano (61).

Based on this hypothesis, we tried a cervical collar for patients when they may have sustained or repeated neck flexion (62). The cervical collar used was a conventional collar used in the treatment of whiplash injury. Patients were advised to wear the collar not to tighten the neck but to keep distance between the jaw and the chest wall. Of the previous 40 patients who had no therapeutic intervention, 25 (62.5%) showed a spontaneous arrest of progression within 3 years of duration, and 34 (85%) within 5 years. Based on this natural course of the

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<th>Year</th>
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<td>1996</td>
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The first author is cited. *Cases of different clinical features are included in the paper.
Comments on Etiology

The etiology of this disease, namely the cause of the dynamic changes induced by neck flexion in adolescence is unknown. The author speculates that disproportionate growth between the vertebral column and the contents of the spinal canal, especially the dural sac during the juvenile growth spurt underlie this phenomenon. This speculation is based on the similarity between the longitudinal growth curve of juvenile Japanese (Fig. 8) (66) and the histogram curve for onset age of the disease (Fig. 1). The peak of the histogram for onset age is approximately 2 years later than the peak of growth curve, which may represent a latent period. Another reason to speculate a delayed growth of the dural sac is that the decrement ratio of the dural sac on neck flexion is inversely correlated to the disease duration or patients’ age. Patients having a disease duration >20 years, or aged >30 years had a significantly smaller decrement ratio (Fig. 6).

Even though the disproportionate growth between the vertebral column and the contents of the spinal canal could be a cause of the disease, the reason why this occurs is still unknown. This mechanism may have an ethnic factor, because the number of such patients is exceedingly large among the Japanese population, and small in Caucasians.

Conclusion

Juvenile muscular atrophy of distal upper extremity affects young people with male preponderance, and causes their functional and social handicaps. It is emphasized that an early detection and a correct diagnosis may lead to therapeutic opportunity to arrest progression or to improve hand disability of young patients.

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