

# Monomelic amyotrophy

## Hirayama's disease

### INTRODUCTION

The patient presenting with weakness and wasting of one limb, usually the arm, can be a considerable diagnostic challenge for the neurologist. While the spectre of the amyotrophic lateral sclerosis form of motor neuron disease (ALS/MND) is often in the clinician's mind, there is also a significant differential diagnosis to be considered. While this article discusses a number of well-known conditions that should be in the differential diagnosis, I will focus particularly on a lesser known condition, Hirayama's Disease (also known as Sobue Disease in North America), that is only rarely seen in European populations and may therefore be less familiar to neurologists outside Japan and India.

Monomelic amyotrophy or 'juvenile non-progressive amyotrophy of the upper limb' is rarely encountered in the general neurology clinics but it may be under diagnosed. Previously thought to be restricted to Japan and South Asia, it is now clear that this condition does occasionally occur in Europe and merits consideration in any patient presenting with pure lower motor neuron weakness of one upper limb. Furthermore the term 'juvenile non-progressive amyotrophy' coined by Hirayama is probably not ideal as it is clear that many cases do progress, albeit extremely slowly. While not obviously treatable, the chief benefit in making the diagnosis is in allaying fears of a much more malignant neurological disorder such as MND.

### HISTORY

The first report of non-progressive amyotrophy of the upper limb appeared in 1959 when Hirayama described 12 patients (Hirayama *et al.* 1959). Subsequently, as larger series of patients were reported from Japan, a distinct clinical entity emerged (Hirayama *et al.* 1963; Sobue *et al.* 1978). Males accounted for over 80% of cases, typically with onset between 15 and 25 years of age. One of the most consistent features through to the present day is the striking unilaterality in the majority of cases, an observation that casts doubt on the plausibility of the spinal cord compressive basis of the condition discussed below. After initial reports it became apparent that the condition was also found not infrequently in the Indian subcontinent (Gourie-Devi *et al.* 1984). Then in recent decades a steady number of cases have been reported from Europe, though relatively few from the UK (de Visser *et al.* 1988; Serratrice 1991). As the disorder became more frequently recognized it is now apparent that onset can be in later life and with a higher frequency in women than hitherto appreciated (van den Berg-Vos *et al.* 2003). And as the debate about whether this condition represents a focal form of primary lower motor neuron degeneration (i.e. a focal form of spinal muscular atrophy), or the local consequence of anatomical variation in the cervical spine continues, the terminology used has become if anything more confusing with Japanese authors now favouring the term 'cervical poldystrophy'.

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### CLINICAL PRESENTATION

In contrast to other lower motor neuron disorders such as spinal muscular atrophy, monomelic amyotrophy is essentially a sporadic, not a genetic condition. In all series reported from Asia to date there has been a male preponderance in a roughly 10 : 1 ratio. Although rare in the West, monomelic amyotrophy accounted for 13% of patients seen at a centre for motor neuron disorders in South India over a 10-year period (Gourie-Devi & Nalini 2003).

The onset is insidious over months or years without any history of antecedent trauma or infection. The median age of onset in Asian case series is in the early 20s but with a broad range extending from 15 to 35 years. However, in a large Dutch retrospective series of lower motor neuron disorders, 16/49 patients had a condition with the same clinical features as Hirayama's monomelic amyotrophy, with an age of onset ranging from 18 to 65 and with a 1.5 : 1 male to female ratio (van den Berg-Vos *et al.* 2003). Whatever the aetiological relationship of the conditions described in these different series, this suggests that the clinical syndrome of monomelic amyotrophy may be more common than previously appreciated in Europe and have a much later onset, well into the age range at which MND commonly presents. While it is usually stated that there are no upper motor neuron features and that the cranial nerves are never involved, if case ascertainment is defined using these exclusion criteria, all such state-

ments carry a self-fulfilling circularity. Tendon reflexes can be reduced, normal or even exaggerated.

The wasting and weakness characteristically involves muscles innervated by the C7-T1 segments. Thus the shoulder girdle is usually spared and there is often a striking sparing of brachioradialis (C5,6) in the forearm, giving rise to an appearance which Hirayama called 'oblique amyotrophy'. Fasciculations appear to be rare. In the most extensive long-term follow up to date, Gourie-Devi and Nalini showed that within a few years progression appears to arrest and patients followed up for more than 20 years never go on to develop progression to other areas of the motor system. In addition to weakness and wasting, patients have described worsening of their symptoms in cold weather.

### DIFFERENTIAL DIAGNOSIS OF THE WEAK AND WASTED UPPER LIMB

Clearly any patient with unexplained weakness and wasting of the upper limb merits MR scanning of the cervical and upper thoracic spinal cord to exclude a structural lesion, either intrinsic or extrinsic. The absence of sensory symptoms does not exclude a compressive myeloradiculopathy. Some patients undergoing surgery for apparent thoracic outlet syndrome continue to slowly progress, suggesting that focal motor neuron degeneration may have been responsible for their symptoms (Donaghy *et al.* 1999).

Somewhat confusingly, one of the most common presentations of MND is with weakness and wasting of one limb, either foot drop or wasting of the small muscles of the hand. It will be apparent from the above clinical description that there are some features in the clinical pattern of Hirayama type monomelic amyotrophy that make the distinction from MND relatively straightforward after a period of time has elapsed. Most notably MND is by definition a more progressive disorder. Fasciculations are common and proximal muscle wasting is often present within months of distal wasting appearing. However, there is no doubt that a monomelic onset of MND can remain confined to one limb for considerable periods of time, even years. This is further complicated by the fact that motor neuron disease restricted to the upper limb (so-called 'brachial amyotrophic diplegia') is characteristically of slower progression than typical MND, often running a clinical course of 5–10 years. In most cases the latter disorder becomes bilateral soon after onset and involves more widespread proximal muscle groups than the more distal and restricted pattern outlined above for monomelic amyotrophy. Most specialists in motor neuron disorders would probably agree that progression to MND can only conclusively be excluded if there is no progression beyond the upper limb within three years. However, at least the recognition that relatively non-progressive forms of weakness and wasting of one limb do exist should help avoid a premature diagnosis of MND. Clinical neurophysiology may be helpful in demonstrating the more widespread involvement of limb or bulbar muscles in MND, but minor EMG changes should never be used to secure the diagnosis if the clinical pattern is not consistent.

The spinal muscular atrophies (SMA) are a heterogeneous group of diseases of genetic origin and variable distribution characterized by slowly progressive pure lower motor neuron degeneration (Talbot & Davies 2003). Despite the presumed hereditary basis of most forms of lower motor neuron degeneration, apparently sporadic cases do occur, though autosomal recessive inheritance is difficult to exclude. A particular form of dominantly inherited distal SMA, which has recently been shown to be due to mutations in the glycyl tRNA synthase gene, shows predilection for the upper limbs. Anita Harding coined the term 'chronic asymmetrical spinal muscular atrophy' to describe a group of patients with distal weakness and wasting, predominantly of the upper limb (Harding *et al.*

### CAUSES OF UNILATERAL WASTING OF THE UPPER LIMB

- Monomelic amyotrophy
- Motor neuron disease/amyotrophic lateral sclerosis
- Spinal muscular atrophy
- Cervical cord structural lesion, intrinsic or extrinsic
- Brachial neuritis
- Multifocal motor neuropathy with conduction block



The patient with unilateral or asymmetrical upper limb wasting presents a diagnostic challenge.

1983). It is possible that some of these patients had a Hirayama-like amyotrophy.

While the overwhelming majority of patients with neuralgic amyotrophy or brachial neuritis present with characteristic deep shoulder aching dysaesthesia, very occasional cases are seen with a near painless onset. The subacute onset and good prognosis for full recovery, along with electrophysiological evidence of widespread brachial plexus involvement, should resolve any diagnostic difficulty.

Multifocal motor neuropathy with conduction block is an important condition to consider in any patient with an apparently isolated lower motor neuron syndrome of the upper limb. In addition to the finding of conduction block on electrophysiological testing, the diagnosis can be suspected when there is weakness out of proportion to any wasting. A characteristic clinical finding is onset with weakness of finger extension.

## PATHOGENESIS

The aetiology of monomelic amyotrophy remains unexplained. Because of the relatively benign outcome of this condition it was not until 1987 that the first description of pathology appeared (Hirayama *et al.* 1987). This and subsequent reports have suggested that there is a focal loss of motor neurons without any associated degenerative changes in the spinal cord to suggest a compressive cause. However, recent reports from Japan have argued a model where focal venous ischaemia arises through compressive flattening of the lower cervical cord due to forward displacement of the cervical dural sac and spinal cord induced by recurrent neck flexion (Hirayama & Tokumaru 2000). It is not clear why this should give rise to a disorder that is relatively non-progressive, so frequently unilateral and so exclusively a lower motor neuropathy, sparing the long tracts. At least one other imaging study has shown no difference in the anteroposterior cord diameter between patients and controls supporting the notion that the aetiology is in fact a primary degeneration of motor neurons (Willeit *et al.* 2001).

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## CONCLUSIONS

- A patient who presents with wasting and weakness of one upper limb, at any age, requires rapid investigation to exclude a structural lesion in the neck.
- When imaging is normal the question of motor neuron disease is inevitably raised, but the message of this article is that there is a significant differential diagnosis to be considered, which includes much more benign conditions.
- Monomelic amyotrophy is a focal motor neuron disorder, with slow progression and apparent arrest after a few years. It may be commoner in European populations than previously appreciated. If the diagnosis is not recognized patients will frequently be inappropriately labelled as having MND and suffer the distress of believing they have a progressive and invariably fatal disorder.

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