Progressive sudomotor dysfunction in amyotrophic lateral sclerosis

M Beck, R Giess, T Magnus, I Puls, K Reiners, K V Toyka, M Naumann

Autonomic dysregulation is part of the complex degenerative process in amyotrophic lateral sclerosis (ALS). To investigate this, sweating was examined at rest in 39 patients with ALS in comparison with a control group. Sweat was collected over a 30 second period over the thenar and hypothenar eminences and on the sole of the foot, using a commercial device based on vapour pressure gradient. The measurements were repeated after three and six months in 10 patients for longitudinal analysis. In early ALS, patients had significantly higher skin water loss than control subjects over the thenar and the hypothenar eminences. In advanced disease stages, sweating was decreased at all sites compared with controls. A significant decline in sweat secretion of about 40% was found over a six month period. The findings suggest an abnormal sympathetic activity with hyperhidrosis in early ALS and a reduction in sweat production as the disease progresses.

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Postmortem histology shows neuronal degeneration in Onuf’s nucleus in the ventral horns of the spinal cord, indicating alterations in bowel and bladder innervation. Although autonomic symptoms in ALS are usually subclinical, these findings suggest that ALS may be a multisystem degenerative disorder.

Our aim in this study was to make a quantitative analysis of sudomotor regulation in ALS patients at different stages of their disease and to see whether there was evidence of a progressive deterioration in function.

METHODS

Thirty nine patients with probable or definite ALS according to the El Escorial criteria (mean (SD) age 55 (8) years, male to female ratio 0.77, disease duration 20 (8.8) months) and 39 healthy control subjects of comparable age (52 (16) years) and female ratio 0.77, disease duration 20 (8.8) months), the patients had significantly higher skin water loss than control subjects over the thenar and the hypothenar eminences. In advanced disease stages, sweating was decreased at all sites compared with controls. A significant decline in sweat secretion of about 40% was found over a six month period. The findings suggest an abnormal sympathetic activity with hyperhidrosis in early ALS and a reduction in sweat production as the disease progresses.

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Sudomotor dysfunction in ALS

**Table 1** Results of quantitative sudomotor analysis

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<td>Control</td>
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Values are mean (SD).

**Figure 1** Progressive sudomotor dysfunction over a six month period (***p < 0.001). Measurements were performed in 10 equally disabled patients with amyotrophic lateral sclerosis and repeated twice at three month intervals over a follow up period of six months. The data represent mean values of water loss recorded at a frequency of 0.5 Hz over 30 seconds. Results were automatically extrapolated and are shown in g/m²/h. Mean values (horizontal bars) are shown, with range (grey area) and 2SD (vertical bars).

**DISCUSSION**

In the early stages of ALS, we found increased sweating on the palm and reduced sweating on the sole of the foot. In advanced stages of the disease, sweating was reduced at both sites. In longitudinal studies, progression of the autonomic disturbance paralleled motor dysfunction with advancing disease.

With our protocol, we avoided the measurement bias that may be introduced by various factors influencing autonomic function. Room temperature, body temperature, activity, diseases such as thyroid disorders, emotional stress, certain drugs, and smoking are all important factors that can affect autonomic activity. We found that assessment of sweat rate using vapour pressure gradient analysis was a safe and reliable technique. Secondary factors such as immobilisation and muscular atrophy that could affect sweat production were unavoidable but more than one recording site was chosen to diminish bias.

Higher sweat rates shortly after disease onset may indicate denervation hypersensitivity of the sweat glands or a higher autonomous neural firing rate. Chida et al reported augmented sympathetic and decreased parasympathetic function in early ALS,1 while Shindo et al found a higher sympathetic firing rate in microneurographic measurements of muscle sympathetic nerve activity in mildly disabled ALS patients compared with other neuromuscular disorders; their patients had only mild to moderate bulbar signs and were able to walk unaided. Thus those results are in keeping with our finding of an increased sweat rate in mildly affected patients, indicating higher sympathetic activity in the early disease stages, and a reduced sweat rate in advanced disease, suggesting a progressive deterioration of the sudomotor system. Degeneration of postganglionic parasympathetic fibres may cause also atrophy of the sweat glands and resulting hypohidrosis. These findings are in line with earlier electrophysiological studies showing abnormal sympathetic skin responses in late ALS, which indicated postganglionic sympathetic dysfunction affecting epidermal and dermal structures.11 They are also in line with the results of pathological studies indicating involvement of the peripheral sensory and autonomic nervous system.12

Impaired sweating occurs in other peripheral and central neurodegenerative diseases13—15—for example in multiple system atrophy and progressive autonomic failure, both postganglionic and preganglionic degeneration has been shown to be responsible for hypohidrosis.16 In hereditary sensory autonomic neuropathy, postganglionic degeneration has been shown by sympathetic skin response studies. However, published reports on increased sweating at early disease stages are lacking.

While autonomic dysfunction does not play a major clinical role in patients suffering from ALS, its presence supports the view that ALS is a multisystem disorder. Patients often report increased or reduced sweating of their hands or feet, reduced skin temperature, or skin discoloration. Skin biopsies have demonstrated abnormal collagen texture and atrophy of epidermal structures including the sweat glands.17 Small blood vessels show ultrastructural changes such as duplication of the basal membranes and deposition of β amyloid. Moreover, electrophysiological and histopathological changes in the sensory system18 indicate a multisystem disorder. We did not perform skin biopsies to demonstrate loss of terminal autonomic nerve fibres directly, because this would have been too invasive. It is thus uncertain how much of the progressive hypohidrosis is caused by structural damage and how much by loss of function in existing nerve fibres.

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