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Sensory involvement in motor neuron disease: further evidence from automated thermal threshold determination

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SUMMARY Thermal thresholds were determined in 40 patients with motor neuron disease and in 40 age- and sex-matched healthy subjects. The thermal thresholds were estimated on the skin of wrist and ankle using an automated microprocessor controlled system and the "two alternative forced-choice method" of psycholphysical analysis. Abnormalities of thermal thresholds (≥99th percentile) were seen in 80% of the motor neuron disease patients. The results are in agreement with reports of sensory pathway involvement in the literature. Thermal threshold abnormalities are common in motor neuron disease and indicate the involvement of the small fibre afferent pathways.

Most authorities consider motor neuron disease to affect exclusively the motor system. Subjective sensory symptoms are however not uncommonly reported and variously described as paraesthesiae, coldness, prickling, numbness, aches and pains.[1–5] Objective sensory abnormalities in contrast are rare[3–5] but nevertheless occasional reports of objective dysfunction have appeared implicating all modalities including pain and temperature sensation.[6–9]

At necropsy, degeneration of posterior columns[1 2 7 10–14] and anterior and lateral columns of the spinal cord outwith the cortico-spinal tract,[6 12–15] loss of neurons in the posterior horns,[1 2 11 13 16] abnormalities in the parietal lobe,[1] degeneration in the thalamus[14] and abnormalities in the posterior root ganglia and dorsal roots[2 16] have been described. Pathological abnormalities in peripheral sensory pathways have also been found[2] and Dayan *et al* 1969 have demonstrated primary Schwann cell damage in sensory nerves.[17] Shahani *et al* 1971,[18] found evidence of abnormal resistence of peripheral sensory nerves to ischaemia in most patients with motor neuron disease. The literature therefore supports the possibility of both peripheral and central sensory abnormalities in these patients, albeit mild when compared with those of the motor system. They are as a rule of insufficient severity to produce clinically detectable changes of sensation[3–5] or significant abnormalities using conventional electrophysiological techniques.[19 20] In a single study, however, one of 13 patient with motor neuron disease, had an absent median sensory nerve action potential as an isolated finding and minimal impairment of vibration sense and two point discrimination.[21]

More sophisticated quantitative techniques have demonstrated abnormalities of touch-pressure, vibration and thermal cooling sensations in a small number of patients.[2 22] In a recent study,[23] two-thirds of motor neuron disease patients had abnormalities of somatosensory evoked potentials and in one-third of these, the abnormalities were thought to arise in the peripheral sensory pathways.

The above observations suggest that more sophisticated techniques for the quantification of sensation might provide further confirmation and a higher incidence of dysfunction in the sensory pathways in patients with motor neuron disease. The purpose of this study was to use such a technique (The Glasgow thermal system[24]) to define thermal thresholds in motor neuron disease as an index of sensory dysfunction and to quantify the severity of this dysfunction.

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Table 1 *Summary of clinical data of 40 motor neuron disease patients*

	Number		*Percentage*	
Type amyotrophic lateral sclerosis		*37*		
Progressive muscular atrophy		*3*		
Cramps (total)		*34*		*85%*
lower & upper limbs	27		67·5%	
lower limbs (LL) alone	7		17·5%	
upper limbs (UL) alone	0			
Muscle wasting (total)		*33*		*82·5%*
UL > LL	18		45%	
LL > UL	6		15%	
both nearly equal	9		22·5%	
Bulbar weakness (total)		*10*		*25%*
mild	6		15%	
moderate-severe	4		10%	
Fasciculations (clinically overt) (total)		*31*		*77·5%*
tongue alone	1		2·5%	
tongue (total)	16		40%	
generalised	8		20%	
Sensory symptoms (total)		*19*		*47·5%*
ache	15		37·5%	
paraesthesia	10		25%	
coldness of extremities	9		22·5%	
abnormal heat	4		10%	
numbness	7		17·5%	

While some patients spontaneously volunteered the occurrence of cramps and sensory symptoms, most did not but did confirm their presence on direct questioning. Sensory symptoms were recurrent and each bout lasted for about 15 minutes.

Patients, controls and methods

Forty patients with motor neuron disease were included in this study. Their age ranged between 36 and 73 (mean = 56·7, SD 11·2) years. There were 25 male and 15 female patients. This sex ratio of 1·6:1 is in agreement with most other published series.[1 22 25] The duration of the symptoms varied between 2–72 (mean = 17·1, SD = 16·8) months. In all the patients the diagnosis of motor neuron disease had been made on clinical grounds by the referring neurologist and was confirmed electrophysiologically (EMG and nerve conduction studies) by ourselves using established criteria.[26] In particular, no patient, with objective sensory abnormality or abnormality of sensory action potential was included. Any cases which did not fully satisfy our clinical and electrophysiological criteria were excluded from the study. All the patients were ambulant, well nourished and none of them had severe paresis of any limb. In wasted limbs, the possibility of entrapment neuropathy was excluded electrophysiologically. None had a family history of neuromuscular disease. All the patients were fully informed of the nature and the purpose of the investigation undertaken. The clinical data of the 40 motor neuron disease patients is summarised in table 1.

The control group consisted of 40 healthy age- and sex-matched subjects. The age and sex distribution of the control and the motor neuron disease group is presented in table 2.

Heat threshold (HT) and cold threshold (CT) values were determined for the volar aspect of the right (R) wrist just proximal to the distal wrist crease and for the medial aspect of the right ankle behind the medial malleolus. These were expressed in °C from the basic skin temperature (before application of the stimulus) using a microprocessor controlled system and the two-alternative forced-choice method of psychological analysis.[27] The method has been described in detail in a previous paper,[24] but the following is a précis of the technique. The microprocessor system controls the stimulating probe (the thermode) and performs the forced-choice trials. The thermode is constructed from an array of semiconductor thermo-electric elements with a stimulating surface area of 12·5 cm² and operates on the Peltier principle. On the background of a constant skin temperature (34–35°C), the thermode applies a quantified thermal (heat or cold) stimulus to the skin tested. The subject is placed in a comfortable position so that the thermode is applied with a standard pressure. A number of trials are performed. In each trial, the subject is presented with two periods during which a null stimulus and an actual thermal stimulus is applied and the periods are indicated to him by two lights in sequence. The order of assignment of the actual and the null stimuli to the periods is randomised by the microcomputer and is unknown to the subject and the examiner. At the end of each trial the subject must choose that period during which he/she felt or thought he/she felt the stimulus. Depending on the response, the computer will alter the stimulus strength applied during the next trial according to the up-and-down transform rule (UDTR).[28] The stimulus power is kept constant such that the rate of change of temperature at the skin surface is 1°C/s. The strength of the

Table 2 *Age and sex distribution of motor neuron disease patients and control subjects*

		Motor neuron disease	*Control*
Total No.		40	40
Age range (yr)		36–73	36–73
Age groups	36–49 (yr)	12	13
	50–59 (yr)	8	9
	60–73 (yr)	20	18
Mean Age (yr)		56·7	55·9
SD		11·2	10·9
Sex distribution	Male	25 (62·5%)	25 (62·5%)
	Female	15 (37·5%)	15 (37·5%)

Table 3 *Thermal threshold values for the motor neuron disease patients and the normal control subjects*

Thermal threshold		*Normal subjects (40)*		*Motor neuron disease patients (40)*		*Test of significance*	
		mean	*SD (°C)*	*mean*	*SD (°C)*	*t*	*p*
wrist	HT	0·23	0·06	0·51	0·34	5·13	<0·0001
wrist	CT	0·17	0·05	0·26	0·14	3·83	<0·0001
ankle	HT	1·53	0·68	4·81	2·05	9·61	<0·0001
ankle	CT	0·18	0·06	0·67	1·03	3·00	<0·005

HT = heat threshold. CT = cold threshold

thermal stimuli is altered by changing its duration of application. The threshold is calculated as the mean of at least 12 separate trial values in accordance with the UDTR. The investigation is carried out in a quiet room at a temperature of 22 ± 2°C. HT is determined first followed by CT. The time required to measure both HT and CT for one site is usually 15–20 minutes. All investigations were carried out by the same person (GAJ).

Results

The mean and SD of HT and CT for the 40 healthy control subjects and the 40 motor neuron disease patients are presented in table 3. Since the control group of this study is of significantly greater mean age, the mean values for thermal thresholds are slightly higher than those in our previously published control group.[24] All the thermal thresholds, both HT and CT, were significantly increased in patients with motor neuron disease (table 3).

Abnormality of thermal thresholds was considered to be present when the value in motor neuron disease patients exceeded the 99th percentile. Table 4 provides a summary of the thermal thresholds testing in the 40 motor neuron disease patients. Thirty two of the 40 patients (80%) had an abnormality of one or more thermal thresholds. All patients with abnormal wrist HT and CT had abnormal ankle thresholds. Abnormalities of thermal thresholds were more frequent at ankle (80%) than at wrist (55%) (see table 4).

The figures shows HT and CT values in motor neuron disease patients for wrist and ankle expressed in multiples of the standard deviation (×SD) from control mean values. Ankle HT values were more than 3 × SD above the normal mean in 60% of the patients and ankle CT values were more than 3 × SD above the normal mean in 55% of the motor neuron disease patients. At the wrist, 45% had HT values more than 3 × SD above the normal mean while 12·5% had CT values 3 × SD above the normal mean.

Discussion

Several pathological studies in the literature have demonstrated the presence of degeneration in both central and peripheral sensory pathways in motor neuron disease.[1 2 6 7 10–17] In general these abnormalities are not associated with clinical sensory loss during life but Brownwell *et al*[14] reported one such case in their series where loss of pain and thermal sensation was noted clinically, and at necropsy evidence of anterior and lateral column degeneration, extending outwith the pyramidal tract, was seen. The same authors found degeneration of the central nuclear complex of the thalamus in 53% of their cases while 56% without sensory symptoms had evidence of anterior and lateral column degeneration. Other motor neuron disease patients with abnormality of thermal and pain sensation have been described.[6 9 29] Posterior column degeneration has been much more widely reported,[1 2 7 10–14] as a rule unaccompanied by clinical symptomatology.

Histological abnormalities of large efferent fibres of peripheral nerves was noted by Kawamura *et al*,[16] and Dyck *et al*[2] reported defects of myelination in the afferent fibres in the superficial peroneal and sural nerves. Primary segmental demyelination in the sural nerve was observed by Dayan *et al*[17] in eight of 10 patients.

Our results indicate that dysfunction in the small fibre thermal pathways is a frequent occurrence in motor neuron disease. Of the 19 patients with sensory symptoms, 18 (95%) had abnormal thermal thresholds while 14 of 21 without sensory symptoms showed qualitively similar abnormalities. Since our technique tests the integrity of both peripheral and

Table 4 *Summary of thermal thresholds testing results in 40 patients with motor neuron disease*

	number	*percentage*
One or more TT abnormal	32	80%
Ankle HT and/or CT abnormal	32	80%
Wrist HT and/or CT abnormal	22	55%
Ankle HT abnormal	24	60%
Ankle CT abnormal	22	55%
Wrist HT abnormal	18	45%
Wrist CT abnormal	5	12·5%

TT = Thermal thresholds
HT = Heat threshold
CT = Cold threshold

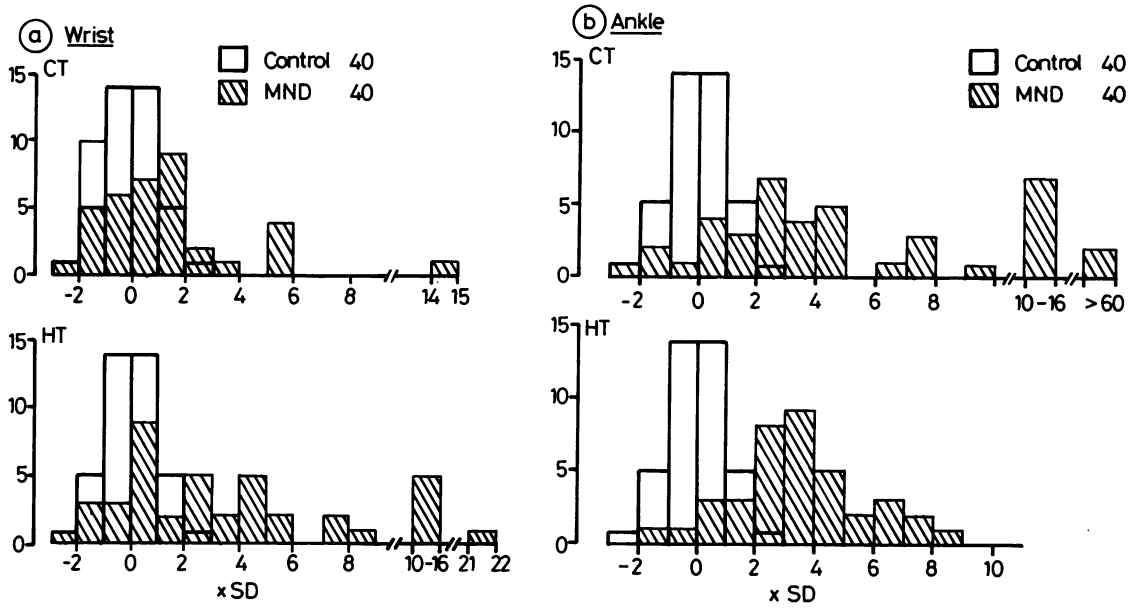

Fig *Thermal thresholds in 40 control subjects and 40 patients with motor neuron disease. (A) Heat threshold (HT) and cold threshold (CT) values for the wrist, (B) HT and CT values for the ankle. Each thermal threshold value is expressed as a figure representing the number of standard deviations (×SD) from the mean control value. Vertical axis = number of patients or controls. Horizontal axis = number of SDs greater or less than the normal control mean.*

central thermal pathways the site of dysfunction can not be determined.

It is unlikely that thermal thresholds are influenced by the degree of muscle wasting in these patients as wasting in general was not severe, the sites of thermal testing did not overlie sites of marked muscle wasting and wasting was more severe in the upper limbs in which abnormalities of the thermal thresholds were least marked. In a separate study of four patients (two with spinal muscular atrophy and two with old poliomyelitis), where there was severe muscle wasting, thermal thresholds were normal. Finally, we found no correlation between the age of the patient, the duration of clinical symptoms and the severity of abnormality of thermal thresholds.

It is concluded that whether arising centrally of peripherally, abnormalities of thermal thresholds are common and are indicative of involvement of small fibre afferent pathways in patients with motor neuron disease.

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