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Neuromuscular paralysis in *vipera aspis* envenomation: pathogenetic mechanisms

Vipera aspis is the most common agent of snake envenomation in Italy and Western Europe.¹ Its bite affects coagulation and causes a shock syndrome with severe cardiovascular failure.

Neurotoxicity, clinically characterised by external ophthalmoplegia, is uncommon (two cases out of 205 patients bitten by *vipera aspis*)¹ and difficult to explain because overt neurotoxic substances have not been detected in *vipera aspis* venom.² Our case suggests that the venom is neurotoxic.

A 20 year old herpetologist was bitten by a *vipera aspis* at the distal extremity of the index finger of the left hand. When he was admitted to the intensive care unit (30 minutes later) he was unconscious (Glasgow Coma Scale 7), pale, tachycardic (170 beats/min), tachypnoeic (50 breaths/min), without detectable peripheral pulses and blood pressure. There was a metabolic acidosis (pH 7.26) and disseminated intravascular coagulation. The left hand was oedematous. Centrifugal venous compression was applied on the left arm. Shock, metabolic failure and disseminated intravascular coagulation syndrome were treated with fresh frozen plasma, albumin, dextran, dopamine and adrenaline, NaHCO₃ and heparin iv infusions. Cardio-respiratory function, metabolic balance and consciousness returned to normal within the following three hours.

Neurological examination revealed facial diplegia, pharyngolaryngeal paresis, bilateral ptosis and external ophthalmoplegia, with complete ocular immobility.

The strength of the trunk, limb and respiratory muscles, deep tendon reflexes, plantar and abdominal reflexes, and sensory functions were normal. Symptoms were not modified by iv administration of 10 mg of edrophonium.

Neurophysiological studies of the facial nerves showed a low amplitude muscle action potential (0.9 mv-nv > 3 mv), with normal latency. Repetitive stimulation at low and high frequencies, tetanisation and stimulation with paired stimuli at stimulus intervals of less than 10 ms gave normal responses without signs of neuromuscular transmission defects. Blink reflex showed responses with normal latencies. Similar neurophysiological studies performed on other nerves (median, common peroneal and sural) were normal.

Five days from the onset of the disease the patient improved considerably and after 10 days, neurological examination and neurophysiological tests were normal. He was discharged after 10 days.

The lack of clinical involvement of motor, sensory and cerebellar pathways within the brainstem, together with the normal latency of blink reflex responses in this case, do not suggest an involvement of the brainstem possibly caused by oedema and/or disseminated intravascular coagulation.³

The electrophysiological signs and the quick improvement of the clinical picture also lead us to exclude a neuropathic lesion and to hypothesise that a transient functional block of activation of a number of muscle fibres. This could be related to three possible mechanisms in particular: 1) a neuromuscular block; 2) a direct action on muscle fibres; 3) a block of depolarisation in the terminal portions of a number of motor nerve fibres.

A neuromuscular block may be related either to a presynaptic site of action of the venom, such as beta-bungarotoxin⁴ and antiacetylcholinesterase, or to a postsynaptic site of action, like alpha-bungarotoxin.² None of these substances has been detected in *vipera aspis* and the electrophysiological findings of the reported case are neither consistent with a presynaptic nor a postsynaptic defect of neuromuscular transmission.

A direct myotoxic effect of animal toxin has been related to phospholipase A2 activity, which has been detected in all viperidae venoms so far investigated.² Moreover some authors⁵ suggest that some toxins, like cardiotoxin of *Dendroaspis jamesoni*, can induce muscle fibre necrosis with a structural damage of the subneural apparatus. Nevertheless myonecrotic action is shown to be confined to the site of injection.^{6,7}

The action of the toxin on the terminal portions of motor fibres could transiently block the conduction of a number of motor fibres by preventing their depolarisation. A lesion in this location is consistent with normal tests of neuromuscular transmission and with the rapid recovery of the amplitude of the muscle action potential as observed in our case. This mechanism has been hypothesised also in the neuromuscular paralysis induced by tick envenomation⁸ and by other biotoxins such as tetratoxin.⁹

Why the neurotoxic action of the *vipera aspis* venom appears to remain strictly localised in cephalic muscles remains unexplained. Peculiar physiological characteristics of cephalic motor units might be an explanation.

GIOVANNI ANTONINI
MAURIZIA RASURA
GIORGIO CONTI*
CONSALVO MATTIA*

Department of Neurological Science,
Institute of Anesthesiology and Resuscitation,*
University of Rome "La Sapienza",
Rome, Italy

Correspondence to: Dr Giovanni Antonini, Dipartimento di Scienze Neurologiche, III Clinica Neurologica, Viale dell'Università 30, 00185 Rome, Italy.

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MATTERS ARISING

Comparison of two methods for measuring thermal thresholds

In their recent paper,¹ Drs Levy, Abraham and Reid compare two techniques for measuring thermal thresholds in diabetic neuropathy. On the basis of their results they conclude that there is little to choose between the method of limits and the forced choice procedure of psychophysical analysis in the determination of thermal thresholds. We believe that their results and the conclusions based thereon are incorrect and a consequence of their experimental design.

When comparing two techniques attempting to measure the same parameter it is imperative that all variables are comparable and strictly controlled since they influence the accuracy of the final results.²⁻⁷ By their own admission the authors have ignored a number of these variables as follows:

- 1) The reference skin temperatures for the Sensortek and Marstock methods are different (30°C and 32°C respectively).^{2,3} Neither is in the optimum range 34-35°C at which the variability of the thermal threshold measurements is minimal.^{6,7}
- 2) The rate of temperature change in the Marstock technique is fixed. By comparison the rate of temperature change in the Sensortek technique, as described by the authors, varies not only during the application of a single stimulus but also for different applications. This is a source of variability.^{3,6,7}
- 3) In the Sensortek technique two stimuli of different modalities are applied to the skin more or less simultaneously; there is a tactile stimulus (when the thermode is applied to the skin) in addition to the specific thermal stimulus. It is particularly important that a pure thermal stimulus is applied without tactile cues as the latter has been shown to modify thermal sensation.⁵
- 4) The duration of application of the thermode is poorly controlled in the Sensortek method. This will influence both the amount and rate of energy transferred to the receptor zone.
- 5) The pressure of application of the thermode to the skin is uncontrolled in both techniques. The authors state that the importance of this factor "in clinical testing has not been systematically investigated". This is incorrect.^{6,7}
- 6) The lack of calibration of heat transfer at the thermode-skin interface in both techniques does not allow for the variability of the thermal properties of the skin.^{8,9}

All these variables except number 3 determine the amount and rate of transfer of energy through the skin to the thermal receptors. The standardisation of this energy transfer is a basic prerequisite for techniques of thermal threshold measurement. Their failure to control these variables invalidates any conclusions on the reliability or otherwise of a single component, namely the psychophysical aspect, of the techniques.

In addition to the technical difficulty the authors choice of subjects further compounds the problem. In diabetic patients thermal thresholds and other parameters of nerve function vary with blood glucose levels,¹⁰ introducing another variable.

Their definition of "static" and "dynamic" methods of application of thermal stimulation is misconceived; dynamic stimuli are applied in both techniques (for example, in the Sensortek method, the temperature of the thermal receptors will alter with time when a thermode of different temperature is applied to the skin surface). The authors' statement, in the discussion, that differences between these two techniques are due to the nature of the stimulus (static versus dynamic) has no conceptual or rational basis.

In conclusion, the authors have not assessed the merit of the two psychophysical procedures, rather they have compared two techniques for thermal threshold testing, which incorporate among many other variables, two different psychophysical procedures. Their conclusion as to the efficiency or otherwise of the psychophysical aspect of the two techniques is invalid.

GORAN A JAMAL
Department of Neurology
STIG HANSEN

West of Scotland Health Boards,
Department of Clinical Physics and Bioengineering
JOHN P BALLANTYNE
Department of Neurology,
Institute of Neurological Sciences,
Glasgow

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Levy et al reply:

Dr Jamal and his colleagues argue that we are unable to comment on the relative advantages

of the two algorithms used for testing thermal sensation as we did not control for a number of confounding variables that influence the rate of heat transfer through skin. This was not the aim of our study; we set out to compare, in a routine clinical setting, two commercially available methods. The algorithms used were one of many differences between the two methods. We simply made the point that in screening studies the choice of a suitable apparatus need not be determined by the psychophysical basis of the test; this is evident from the similar coefficients of variation of all comparable methods.

Dr Jamal's long excursion into the factors influencing transfer of thermal energy is irrelevant since control of stimulus-related factors other than skin temperature and site would have materially altered the methods from those which are commercially available, and does not affect our proposition that precision and reproducibility are related neither to the choice of apparatus nor to the algorithm used. It is our contention that the high variability of all clinical psychophysical methods owes more to "central processing" than to the standardised presentation of the stimulus.¹ Our experience with the Glasgow thermal testing method (as used in the Medelec instrument) showed that it was no more reproducible than three other methods, a finding which is at variance with Dr Jamal's claim of "negligible" intraindividual variability.²

Some of the technical points raised by Dr Jamal apply equally to both methods, so we are unclear how they would affect a comparative study (for example, the surface skin temperature, the lack of calibration of heat transfer at the thermode, the thermode application pressure, and the fact that both methods involve application of uncontrolled tactile stimuli). As to the question of thermal neutrality, Kenshalo³ found that it could be achieved over a wide range of temperatures, 29-37°C; Dr Jamal's advocacy of the use of a basal temperature of 35°C is therefore arbitrary and in addition quite impractical and time-consuming to achieve in diabetic patients, many of whom have peripheral small- and large-vessel disease. The criticism of our use of diabetic patients on the basis of the known effects of ambient blood glucose levels on nerve function is misplaced in a paper devoted specifically to a clinical study of diabetic patients. In addition, in a large group comparison, the effects of blood glucose variation can also be discounted.

A study comparing algorithms alone with control of all stimulus-related factors has yet to be done and remains a formidable challenge. We are yet to be convinced that strict attention to details of presentation of the thermal stimulus is relevant to the testing of thermal sensation in untrained subjects in clinical settings.

DAVID LEVY
RALPH ABRAHAM
GORDON REID
Department of Diabetes and Endocrinology,
Central Middlesex Hospital,
London NW10 7NS

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Responses to temperature in primary hypothyroidism

Using standard neurophysiological criteria Beghi *et al*¹ made a definite diagnosis of polyneuropathy in 72% of 39 consecutive outpatients with primary hypothyroidism. They took care to maintain skin temperature at 32-34°C throughout these studies, but do not comment upon core temperatures.

It is well recognised that hypothyroid patients may be hypothermic.² In 1983 we found similar abnormalities in peripheral nerve conduction in hypothyroid patients.³ We also corrected skin temperature in these studies. Central conduction velocity in the visual pathways, represented by latency of the visual evoked potential, was also slow. These abnormalities were reversed by thyroxine. However, we also demonstrated that correction of hypothermia by central warming led to a rapid improvement of both of these neurophysiological parameters in untreated patients.

Beghi *et al* state that using physiological criteria the prevalence of polyneuropathy in hypothyroidism is 718 cases per 1000. Our data suggest, however, that these abnormal conduction velocities are, in many cases, appropriate physiological responses to a reduced core temperature rather than due to pathology of the peripheral nerves.

RJ ABBOTT
BP O'MALLEY
Leicester Royal Infirmary,
Leicester LE1 5WW

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Management of intraventricular haemorrhage secondary to ruptured arteriovenous malformation in a child with von Willebrand's disease

The recent report by Osenbach *et al*¹ about a 13 year old girl with von Willebrand's disease and an intracranial arteriovenous malformation raises some important issues.

Their patient developed intraventricular and subarachnoid haemorrhage following minor trauma. Although a bleeding diathesis was diagnosed, a structural vascular lesion was suspected and subsequently confirmed by angiography. The occurrence of an arteriovenous malformation in a patient with von Willebrand's disease is of interest in view of the possible association of this bleeding disorder with various cardiovascular abnormalities, including mitral valve prolapse,² arterial aneurysms,³ gastrointestinal angiodysplasias,⁴ and telangiectasias.⁵

It has been suggested that this association represents an underlying mesenchymal disorder of von Willebrand's disease, resembling the heritable connective tissue disorders.^{2,4} Abnormalities of the mesenchym derived extracellular matrix may be the common ground of, among others, von Willebrand's disease, Ehlers-Danlos syndrome, polycystic