Neurovascular 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 cardiovasculard failure.

Neurotoxicity, clinically characterised by external ophthalmoplegia, is uncommon (two cases out of 205 patients bitten by vipera aspis) 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), with 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. Cardiovascular, 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, mv > 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 with no significant neuromuscular transmission defects. Blink reflex showed responses with normal latencies. Similar neurophysiological studies performed on other nerves (medial, 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 dissemi-

nated intravascular coagulation.

The electromyography signs and the quick improvement of the clinical picture also lead us to exclude a neuropathic lesion and to hypothesis 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-bungarotoxin3 and antaceptylolisterase, or to a postsynaptic site of action, like alpha-bungarotoxin.4 None of these mechanisms 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 viperid venom so far investigated.5 Moreover some authors6 suggest that some toxins, like cardioxotin of Dendroaspis janesmis, can induce muscle fibre necrosis with a structural damage of the subsarcolemmal apparatus. Nevertheless myonecrotic action is shown to be confined to the site of injury by the authors.

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 envenomation7 and by other biotoxins such as tetrodotoxin.

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.
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 choose of subjects further compounds the problem. In diabetic patients thermal thresholds and other parameters of nerve function vary with blood glucose levels, 1 incorporating which procedures, these two parameters are interrelated to the nature of the subject. The authors' statement, in the discussion, that differences between these two groups 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 use of these psychophysical procedures, rather they have compared the two techniques for thermal threshold testing, which incorporate among many other variables, two different psychophysical procedures. This conclusion as to the efficiency or otherwise of the psychophysical aspect of the two techniques is invalid.

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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, including 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 clinically 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, as this is evident from the similar coefficients of variation of all comparable methods.

Dr Jamal's long excursus 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 support 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 stems 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 more reproducible than the other methods. We agree that this is at variance with what Dr Jamal's claim of "negligible" intrindividual variability.

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, Keshalso1 found that it could be achieved over a wide range of temperatures, 25-37°C; Dr Jamal's advocacy of the use of a basal temperature of 35°C is 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; it is 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.

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Responses to temperature in primary hypothyroidism

Using standard neurophysiological criteria Beghi et al made a definite diagnosis of hypothyroidism in 72% of 39 consecutive outpatients with primary hypothyroidism. They took care to maintain the 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.7 In 1983 we found similar abnormalities of skin 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 marked improvement of both these neurological parameters in untreated patients.

Beghi et al state that using physiological criteria the prevalence of hypothyroidism is 718.3. The data suggest, however, that these abnormalities in conduction velocities are, in many cases, appropriate physiological responses to a reduced core temperature rather than due to pathology of the peripheral nerves.

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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 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 mural 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.4 6 Abnormalities of the mesenchymal extracellular matrix may be the common ground of, among others, von Willebrand's disease, Ehlers-Danlos syndrome, polylicystic