Neurovascular paralysis in *viperas aspis* envenomation: pathogenetic mechanisms

Vipera aspis is the most common agent of snake envenomation in Italy and Western Europe. 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 *viperas aspis*) and difficult to explain because overt neurotoxic substances have not been detected in *viperas aspis* venom. Our case suggests that the venom is neurotoxic. A 20 year old herpetologist was bitten by a *viperas 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 2), 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. 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 oucular 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 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 sign 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.

The electrodiagnostic 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-bungarotoxin and anticholinesterase, or to a postsynaptic site of action, like alpha-bungarotoxin. None of these mechanisms has been detected in *viperas 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. Moreover some authors suggest that some toxins, like cardiotoxin of *Dendroaspis janesium*, 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.

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 envenomation and by other biotoxins such as tetratoxin.

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

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