Harlequin syndrome: does a cranial autonomic neuropathy influence headache?

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The paper by Viana et al analyses the relationship between Harlequin syndrome and headache. One facet of this interesting syndrome is the demonstration of pupillary signs by pharmacological studies explicable by the sudden onset of parasympathetic and sympathetic deficit, implicating an autonomic neuropathy mediated by an autoimmune process or viral infection.1

Sympathetic innervation of human cerebral and extracranial circulation is well documented. Parasympathetic innervation of cranial arteries has been established in rat, cat and monkey, but information on humans is meagre. Stimulation of the pre- or post-ganglionic fibres of the sphenopalatine ganglion in animals increases cerebral blood flow, probably via orbital rami from the ganglion looping back to the internal carotid artery, and projecting directly to the external carotid artery.2

A clinical marker of parasympathetic activity in man is the redness and lacrimation of the ipsilateral eye and discharge from the nostril in most episodes of cluster headache and some of migraine, during which the outflow of vasoactive intestinal polypeptide is enhanced in the ciliary ganglion, post-ganglionic distribution to the pupils through short ciliary nerves. Facial parasympathetic fibres are derived from the superior salivatory nucleus in the brainstem, and synapse in the sphenopalatine ganglion, with post-ganglionic distribution to cerebral arteries, and the vasculature of glands in the eyes, nose and mouth.3 If this autonomic outflow was also affected in Harlequin syndrome, some alteration of headache characteristics might be expected.

Following the classic studies by Harold G Wolff and colleagues that reported frontal branches of the superficial temporal artery dilate on the side affected by migraine headache and subside with the headache after the administration of ergotamine, migraine was regarded as a ‘vascular headache’.4 The pulsatile nature (‘throbbing’) of migraine headache, the bulging of preexisting burr holes at the height of headache, and relief by compression of cranial arteries has been established in many cases of Harlequin syndrome with accompanying autonomic failure.5,6

Parasympathetic pre-ganglionic fibres for the eye originate in the Edinger-Westphal nucleus of the midbrain, and travel with the oculomotor nerve to the ciliary ganglion where they synapse with post-ganglionic distribution to the pupils through short ciliary nerves.7 In general terms, any physical or pharmacological agent that dilates cranial vessels could intensify pain.8 Of the eight case histories analysed by Viana and her colleagues, three patients had headache during the unilateral flushing due to exertion, but one was contralateral to the flushing side. Recurrence of headaches with migrainous features in the other five cases reported was not related to the episodic flushing of Harlequin syndrome.

The authors conclude from this interesting study that migraine and Harlequin syndrome are pathologically independent. The lack of any correlation suggests that the cranial parasympathetic deficit in Harlequin syndrome is limited to output from the ciliary ganglion, and that there is no significant interference with cerebrovascular innervation.

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