

A MODERN PERSPECTIVE ON SOME OF THE MOST HIGHLY CITED JNNP PAPERS OF ALL TIME

Observations on 500 cases of migraine and allied vascular headache

James W Lance



Migraine: the clues were there 50 years ago, suggests James W Lance, Professor Emeritus of Neurology, University of New South Wales, Sydney



EDITOR'S
CHOICE

In the 1950s, before the Ad Hoc Committee on the Classification of Headache and the more detailed criteria devised by the International Headache Society from 2004 onwards, the separation of headache entities was far from clear.

During that period I had the privilege of having George Selby as a mentor while attending the Northcott Neurological Centre in Sydney. He was a meticulous clinician with a particular interest in migraine, a condition that was in ample supply in that outpatient clinic, which had been established to provide neurological advice to returned servicemen and their families after World War II. Retrospective analysis of data was aided by a set pattern of history taking and typed records.

Why did we refer to 'allied vascular headaches'? The occurrence of severe episodes of headache accentuated by each heart beat was accepted as migrainous in type even though habitually bilateral as it was in 191 of our 500 patients. Visual disturbances and paraesthesiae occurred with generalised headaches as often as hemicrania. Unilateral paraesthesiae were followed by ipsilateral headache as often as contralateral (which would not have been the case were the cortical disturbance responsible for causing headache). In 103 patients, headache persistently

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affected the same side of the head without any underlying structural cause becoming apparent, contrary to popular belief at that time. In 21% of patients, headaches started under 10 years of age and 31% of adults questioned recalled the frequent occurrence of vomiting ('bilious attacks') encountered unassociated with headaches.

A feature in our report that has recently been rediscovered²⁻³ is scalp tenderness (allodynia) experienced during or after the headache by 65% of our patients. This varied in intensity from sensitivity on combing their hair to preventing the sufferer from lying on the affected side at night. The development of allodynia suggests the withdrawal of inhibition of the afferent inflow from cutaneous receptors in line with that from cranial arteries causing the pulsatile nature of the headache, and from the special senses responsible for enhanced susceptibility to light, sound and smells.

True vertigo within the definition of hallucination of movement had occurred in 33% of 217 patients in whom this symptom was sought. Confusion at the height of the attack had been experienced by 14% of patients and some exhibited automatisms or apparently hysterical behaviour.

Another point of interest was that the frequency of headaches increased with emotional factors. In the 15% of patients who reported more than 10 headaches a month, tension headaches were often present as well, making it difficult for patients to distinguish between the two in what is now known as 'chronic migraine'.

Understanding the broad clinical spectrum of migraine encouraged laboratory and clinical studies that followed.

Inspired by observations of Sicuteri in Florence⁴ and Kimball *et al* in New York,⁵ we embarked on studies of plasma serotonin in migraine.⁶⁻⁷ These drew the attention of Dr Patrick Humphrey in England who devised sumatriptan as a selective 5HT_{1B/D} agonist for the acute treatment of migraine. He wrote to me: "Undoubtedly your clinical studies on serotonin were seminal in our discovery of sumatriptan because they were critical in getting me to focus on serotonin rather than prostaglandins. Your observation too, which you confided in me, that sometimes methysergide was effective acutely was also key. They were certainly exciting days".

Following the serotonin trail our team reported that a double blind trial of the serotonin uptake inhibitor amitriptyline proved effective in the relief of chronic daily headache⁸ and presented a pilot study of the monoamine inhibitor phenelzine in the management of intractable migraine.⁹

An animal model linking neural and vascular factors applicable to migraine was put forward as the result of experiments by Goadsby and Lambert in our laboratory.¹⁰ Collaboration between Peter Goadsby in our Sydney laboratory and Lars Edvinsson in Uppsala¹¹ showed that the content of calcitonin gene related peptide was increased in jugular venous blood during migraine headache. Calcitonin gene related peptide antagonists have recently been shown to be effective in acute migraine therapy without causing vasoconstriction,¹² a useful addition to the migraine armamentarium.

Over the past 50 years patients have asked the questions and research has provided some answers. Our quest is continued by Goadsby, now in San Francisco, and by colleagues in Sydney.¹³

In the 1960 paper, Selby and I concluded that the migraine syndrome presents an interesting study for the clinician because of the diversity and severity of its symptoms. "With further research, the time should be closer when the many fragments of knowledge may be joined together into a single concept." Fifty years later one still remains optimistic.

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