Primary headache syndromes may generally be distinguished as being either episodic, such as typical migraine or cluster headache, or chronic, such as chronic tension-type headache (CTTH) or hemicrania continua. In truth it is chronic headache, and most particularly chronic daily headache (CDH) in its various forms, that gives the sub-speciality of headache a bad name. Daily headache in all its manifestations probably effects 5% of the population (Scher et al., 1998; Castillo et al., 1999), of which about half is clear-cut, at least on clinical grounds, CTTH. If neurology is to take headache into the next century, as either necessity or interest dictate, then the common headache syndromes must be adequately understood and it is timely to think about daily headache.

It is on this background that we can greet the positive observations that Olesen’s group report in this issue of Brain (Ashina et al., 1999a), and the similarly challenging therapeutic data recently reported in The Lancet (Ashina et al., 1999b). Two fundamental issues need to be answered in regard to CTTH: the first is its nature or basis, and the second, related issue is how TTH should be handled in terms of nosology. This new work contributes in some measure to both questions.

Crucial to any attempt to improve the management of CTTH in clinical practice is to develop an understanding of what the syndrome actually represents. The International Headache Society (IHS) Diagnostic Classification (Headache Classification Committee of the International Headache Society, 1988) sets out clear operational criteria, but they are essentially nihilistic. The IHS classification says more of what CTTH is not than of what it is: preferably bilateral, non-pulsatile headache without vomiting but perhaps nausea, and with no sensory sensitivity to head movement nor light and sound, although one of the latter pair is acceptable. In this definition system CTTH is little more than lots of episodic TTH, which in turn is lots of not-migraine. Although this is not absolutely true, it does highlight the problems of definition with TTH. TTH can come with and without muscle tenderness, but does that tell us about the nature of that tenderness or its role in the pathophysiology?

Ashina and colleagues have shown us that summary scores for muscle hardness, measured with a remarkably ingenious device of Professor Sakai’s, are reduced by the nitric oxide synthesis (NOS) inhibitor L-monomethyl-L-arginine hydrochloride (L-NMMA), and muscle tenderness is also reduced (Ashina et al., 1999a). Given that L-NMMA is effective at reducing pain (Ashina et al., 1999b), the data support the broad concept that CTTH is, at least in some part, a disorder of the central nervous system with probable sensitization of second-order trigeminal neurons and some peripheral component. Moreover, given that activation of NOS is associated with glutamate (N-methyl-D-aspartate, NMDA) transmission, and the fact that both NMDA and AMPA (α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid) glutamatergic excitatory mechanisms are present in the trigeminal nucleus caudalis of experimental animals (Storer and Goadsby, 1999), one can speculate on the possible role of NO generation in central sensitization (Mao et al., 1997) to explain some part of the CTTH pathophysiology. The results of the new study are perfectly compatible with the pioneering observations of Schoenen and colleagues concerning electrophysiological changes in the brain of patients with chronic headache (Schoenen et al., 1987), which suggested an important central component to CTTH.

Given that there is likely to be trigeminal activation and possibly sensitization of second-order neurons in CTTH, how does that enlighten the clinical definition of the syndrome? The trigeminal nucleus is the common thread that runs through the primary headaches in terms of expression of the pain. As we have seen in recent times from functional brain imaging, primary headache syndromes share pain expression and mediation systems with thalamic, cingulate, insula and frontal cortex activation but have apparently unique areas of activation related to the syndrome, midbrain and dorsal pontine structures for migraine and the posterior hypothalamic grey matter for cluster headache (May and Goadsby, 1999). The relatively bland clinical profile of TTH thus suggests that TTH is heterogeneous in its central causes.

By this concept, two or more syndromes of dysfunction of brain pain-control systems may manifest as a dull, more or less featureless head pain and not be distinguishable on clinical grounds in terms of the pain. The core issue is the contrast of the clinical phenotype with the headache biotype, which the IHS classification (Headache Classification Committee of the International Headache Society, 1988) could not address simply because there were insufficient data. If one accepts that the phenotype that is now called TTH may be due to more than one fundamental neurobiological process then the next step is clear: define the biology.

Biological/phenotypic overlap is likely to be at the core of the controversy concerning CDH, which in its many forms is arguably the single biggest management challenge a neurologist faces. CDH does not describe a single entity, but
is nevertheless a useful term for a group of problems that share daily or near-daily head pain as their core characteristic; it has both primary and secondary causes and associations. The most controversial issue, that of transformed, or what I think is more appropriately called chronic migraine, may simply be migrainous biology, the genetic predisposition to migraine, manifesting as typical attacks or in a less developed form as attacks of what could be called phenotypic TTH. This syndrome is further complicated by issues of medication misuse, which can be parsed away on clinical grounds, when the problem is recognized. If one uses a phenotypic classification system, such as IHS now is, then these patients have two headaches, migraine and TTH, but if one takes a biotypic view, perhaps some patients have one disorder with two manifestations.

What evidence is there for having this biotypic/phenotypic view? The arguments for the existence of transformed or chronic migraine have been well rehearsed elsewhere (Silberstein and Lipton, 1997). The best argument at the moment is probably an epidemiological one. If CTTH and migraine merely co-exist, then the prevalence of that co-existence should be predictable based on what we know of each entity. However, population-based data show that the co-existence is several times more common than it should be and is absolutely consistent with the existence of a form of persistent or chronic migraine (R. B. Lipton, personal communication). In essence the concept is that over time a patient with typical migraine has more frequent attacks, which lose their migrainous features; perhaps sensitization is taking place? This syndrome is often associated with medication misuse, but there is no doubt that patients without medication misuse are seen. A fascinating study of disabling headache has just been presented which adds to this discussion. Lipton and colleagues investigated in a double-blind placebo-controlled multiple-attack study patients with migraine who also had phenotypic TTH, and patients with exclusively TTH (Oral Presentation American Academy of Neurology, March 1999). Sumatriptan 50 mg was equally effective in the first group of patients in their migraine as well as their disabling TTH, but ineffective in TTH in the group without any other headache types. These data provide support for the view that the phenotype TTH in migraine sufferers shares some biology with migraine attacks in those patients, although it must be said is far from proving the argument.

Where are we with CTTH as we leave the twentieth century? Olesen’s group clearly demonstrates with their new investigations that the syndrome is amenable to study (Ashina et al., 1999a, b). The new data suggest, at least as an extension from the biology of basic pain mechanisms, that some form of sensitization with second-order trigeminal neurons is critically involved in the clinical manifestations of CTTH. Moreover, there is even a genetic component to the problem (Russell et al., 1999). These data send out a challenge to researchers in the field to take up the problems of chronic primary headaches and study their biology so that future classifications and nomenclature can be based on better disease understanding. From a clinical standpoint a time is approaching when daily-headache patients, who probably represent the greatest disability that headache can bestow, will move into the warm light of biological understanding that underpins clinical interest and better management.

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References