19 15th Marcia Wilkinson Lecture: Is migraine really a disease

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There are advantages and disadvantages of being a generalist or multi-specialist. The disadvantages relate to not having one field of interest in which to excel and thereby attain higher status. One advantage of being a multi-specialist is the occasional opportunity to transfer lessons learnt in one sphere of interest to problems encountered in another, apparently unrelated, field. Over the past 30 years I have had a number of interests within clinical neurology : headache and migraine, epilepsy, stroke, Parkinson's disease, botulinum toxin and clinical neurophysiology. In this lecture I will explore ways in which developments in one field – epilepsy-can be used to change our thinking about the management of migraine.

We tend to think of migraine as a relatively specific disorder in which patients suffer from recurrent attacks of headache, usually unilateral, accompanied by nausea, vomiting, photophobia and phonophobia and in some cases focal neurological symptoms. It now seems likely that the pathophysiology of migraine aura involves both hyperactivity and then hypoactivity of cerebral cortical neurones, akin to the experimental phenomenon of cortical spreading depression, and that the headache is related to dilatation of cerebral vessels, release of peptides from trigeminal sensory nerves, and probably also some changes in brain stem sensory pathways, tending to increase pain perception. Attacks last from hours to days. It is recognised that many factors and conditions can be responsible for or trigger the clinical presentation of migraine. Genetic factors are frequently suspected, and we now know that at least two different genes (19p13 and 1q23) can underlie different forms of familial hemiplegic migraine, and that about 70% of patients with migraine report the condition in a first-degree relative. Head injury, stroke, vascular

malformations, SLE, mitochondrial disorders, cardiac anomalies, encephalitis, vasculitis, cerebral tumour and arterial hypertension have all been reported to be causes or associations of migraine.

Epilepsy represents a group of disorders in which recurrent episodes of altered cerebral function (seizures) are associated with excessive and hypersynchronous discharge of cerebral neurones. Attacks last from seconds to minutes. Genetic factors are thought to be relevant in about 20% of patients, and are likely to be responsible for the idiopathic epilepsies. Other causes include head injury, stroke, vascular malformations, SLE, vasculitis, arterial hypertension, mitochondrial disorders, encephalitis, hydrocephalus, MS, cerebral tumours and degenerative disorders. The similarities between the causative factors for migraine and epilepsy are striking, and the two disorders show significant co-morbidity. The relative risk of migraine for an epileptic patient is 2.4 and up to 6% of migraineurs (about 10 times the general population rate) have epilepsy. It is interesting to note that several of the anti-epileptic drugs are effective prophylactic agents for migraine – a point that I will return to later. These findings do not necessarily imply that epilepsy causes migraine or vice-verse, but may simply mean that both disorders are different patterns of misbehaviour which the damaged or abnormal brain has at its disposal.

Benign occipital epilepsy, an idiopathic disorder usually seen in childhood, offers a fascinating example of a cross-over condition between epilepsy and migraine. The sufferer experiences attacks of coloured circular visual hallucinations, and sometimes other seizure manifestations, with EEG evidence of occipital spike and wave discharges, often followed by occipital headache and vomiting. The similarity to migraine is so strong that an identical condition was formerly described as “basilar migraine with occipital spike-wave discharges”.

It is interesting and important to take account of the differences between a disease and a syndrome. Patients suffering from a disease show “ a common aetiology and prognosis despite individual modifications”. An

example of a disease is pneumococcal pneumonia. A syndrome is “a distinct group of symptoms and signs which, associated together, form a characteristic clinical picture or entity”. A syndrome may have several different causes: for example, Cushing’s syndrome may be due to pituitary tumour, adrenal tumour or be iatrogenic from corticosteroid treatment. During the 1990’s epilepsy was subjected to a syndromic approach, which now forms the basis of the latest International League Against Epilepsy 2001 classification of epileptic disorders. Some examples of epilepsy syndrome are : idiopathic focal epilepsies of childhood, familial focal epilepsies, symptomatic epilepsies, idiopathic generalised disorders, and so on. This syndromic approach to classification has enabled the recognition of groups of patients who, irrespective of aetiology, show similar features, whose epilepsy tends to respond to certain types of medication, and for whom a prognosis can be given.

Examples of the value of this approach are childhood absence epilepsy and juvenile myoclonic epilepsy. Childhood absence epilepsy is a genetic disorder, presents between 2-10 years of age, has a characteristic 3/second spike and wave generalised EEG pattern during attacks, shows a good response to sodium valproate, lamotrigine and ethosuximide, a poor response to phenytoin and carbamazepine, and is likely to remit by the early teenage years. Juvenile myoclonic epilepsy is also a genetic disorder, with onset at 14-15 years of age, presents with myoclonic limb and body jerks, generalised tonic-clonic seizures and sometimes absences. The EEG typically shows a generalised polyspike and wave pattern. The seizures are best controlled with sodium valproate or clonazepam, but show a poor response or even exacerbation to carbamazepine or vigabatrin. The disorder is life-long and tends not to remit with age.

Migraine could be looked on as a group of syndromes instead of a disease entity. A simple list of migraine syndromes could comprise : attacks without aura , with aura, with hemiplegic aura, with “basilar” aura, menstrual migraine, late onset migraine, and migraine aura without

headache. This type of approach could be applied to clinical problems such as selection of drugs for migraine prophylaxis.

Prophylactic medication is often considered for migraine patients if their attacks are occurring more than twice a month or if less frequent attacks are particularly severe. Courses of treatment are typically taken for 3-12 months. The commonly used groups of drugs are beta-adreno-receptor blockers, 5-HT2 receptor antagonists, anti-epileptic drugs, tricyclic antidepressants and calcium channel blockers. Drug prophylaxis trials show on average approximately 50% reduction in the number of migraine attacks per month in about 50% of patients. Different drugs tend to be selected either at random or because of other factors such as concomitant obesity, hypertension or sleep and mood disturbance. Compared with the expected good control of seizures in 70-80% of epileptic patients on preferred anti-epileptic drug regimes, migraine prophylaxis is disappointing. This may in part be due to poor patient compliance, and the relative lack of efficacy of the drugs currently in use. One other reason may be that we are treating several different types of migraine with the same group of drugs, some of which will be effective and some of which will not. Several different strategies might be used to improve the response to migraine prophylaxis : an empirical approach would be to synthesise new drugs at random, try them all for their efficacy in migraine and move to clinical trials of more promising agents. The ideal purist approach would be to identify the specific gene defect underlying a patient's migraine, define the gene product and change of function, and then design a drug capable of reversing this defect. This approach, although theoretically appealing, might involve several decades of work. An alternative approach would be to view migraine as a group of syndromes, rather than a disease entity. For each clinical syndrome the diagnostic symptoms and signs could be defined, and then large scale clinical drug trials set up to compare the relative efficacy of different available drugs, using a randomised cross-over design and sub-group analysis. This approach would identify the best drugs for the different syndromes and might be expected to take a number of years rather than decades.

To group migraine into a set of clinical syndromes would offer a new way of improving the care of sufferers based on their symptom complexes, rather than assuming a common aetiology. I suggest therefore that migraine should be regarded as a group of related syndromes, typically marked by recurrent attacks of usually unilateral headache, associated with nausea, vomiting, photophobia and phonophobia and in some cases focal neurological symptoms, especially visual disturbances. If the syndromic approach to migraine were to prove as effective in identifying the best treatments for different types of patient as has been seen in the epilepsies, this would represent a significant advance in clinical care for our patients.

Literature

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