Best evidence and the clinical decision making process

The articles by Helfenstein and Newcombe highlight the difficulties faced by clinicians in making a treatment decision for their patient when confronted by contradictory evidence. We are now faced with an ever increasing array of data of variable quality, which all need to be considered, for us to reach the best treatment decision for our patients. Systematic reviews, the cornerstone of evidence based medicine, are an important and increasingly utilized tool that use predefined objective criteria to aggregate data from trials, to provide evidence on which to base clinical decisions. However, systematic reviews have their own problems. Some, such as the finding of increased mortality with the use of intravenous albumin,8 have been controversial and heavily criticised.4 Dr Helfenstein highlights another problem with meta-analysis—that is, depending on the particular choice of the interpretation of an individual trial within a meta-analysis can vary. Most clinicians, like myself, will not be familiar with the statistical techniques utilised in meta-analysis. Thus, the issues highlighted in the two articles2 8 will add further to the confusion felt by many.

Given these problems, what evidence should we rely on to make a clinical decision for our patient? Should the findings of a randomised controlled trial that are contrary to the findings of a meta-analysis take priority in our decision making process? Clearly, there are no simple answers to these questions. We should certainly not go back to the hierarchy proposed: in this model, case reports are at the top end of the scale.5 However, there may be situations where the rigid application of this hierarchy is inappropriate. For example, observational studies may provide evidence that is as good, if not better, than that provided by randomised controlled trials.2

Certainly, this is the current situation when one is focusing on the harms caused by medicines, where randomised controlled trial evidence is singularly absent or unreliable. Similarly, poorly conducted randomised controlled trials, which are then included in a systematic review, can produce erroneous and contradictory results.7 By contrast, a good single randomised controlled trial can over-turn many years of conventional “wisdom” that may have been based on observational data. For example, a meta-analysis of observational studies suggested that hormone replacement therapy (HRT) was associated with a 50% reduction in the relative risk of coronary events.2 Conversely, the single HERs randomised controlled trial found no benefit of HRT in secondary prevention of coronary events.9 The findings of HERS have been supported by angiographic studies,10 and the evidence taken together, has led the American Heart Association to no longer recommend the use of HRT in secondary prevention of coronary artery disease.11 Finally, it is also important to consider whether results from trials, where patient recruitment is often dependent on a long list of specific inclusion and exclusion criteria, are applicable to an individual patient in a real-world situation.12 All these factors therefore have to be considered in making a clinical decision; thus, in my opinion, the answer to the problem highlighted by Helfenstein is not simple,1 but crucially depends on a critical appraisal of the characteristics of the evidence that is available.

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References


Valproate encephalopathy and hyperammonaemia

In their excellent review of non-hepatic hyperammonaemia, Hawkes and colleagues acknowledge the diverse modes of presentation of, and the importance of a high index of suspicion for, encephalopathy secondary to raised blood ammonia concentration.2 We would like to complement their review by reporting the case of a 78 year old woman on valproate encephalopathy associated with hyperammonaemia.

The patient presented to the accident and emergency department with a four week history of acute on chronic confusion, altered personality, and uncharacteristic aggressive behaviour. She had been taking sodium valproate (modified release) 500 mg twice daily and 300 mg at night, in addition to carbamazepine (modified release) 400 mg twice daily, for epilepsy diagnosed 20 years earlier.

On examination, her temperature was 37.5°C. The patient was confused, extremely agitated, and uncooperative. For example, the patient was eventually discharged home on an increased dose of carbamazepine alone (600 mg twice daily) after stopping the sodium valproate, and the patient’s aggression and agitation resolved.

Since 1979, there have been at least 30 cases of sodium valproate associated encephalopathy reported in the specialist neurological and pharmacological literature, however, only two reports have appeared in the general medical literature in English.1 Hyperammonaemia is an important and potentially reversible cause of encephalopathy, and should be suspected in any confused patient on sodium valproate therapy.

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Recurrent orogenital ulcers with papillodema and headaches

I enjoyed reading the self assessment question by Abbas et al published recently. It would be of great interest to know the ethnic background of this 33 year old man. In a study by Daif et al, from Saudi Arabia, Behçet’s disease accounted for almost one fourth of their cases of cerebral venous thrombosis (CVT), likely to be explained by the higher prevalence of Behçet’s disease in the Middle East.

It is imperative that all patients with CVT, even in the presence of a known aetiological factor, have a thorough diagnostic work-up, as multiple factors can be encountered in an individual patient. Also, the factor V gene mutation has been shown to be associated with a sixfold increase in venous thrombosis risk in Behçet’s disease.

Recombinant tissue plasminogen activator, either than urokinase, can be used as a local thrombolytic agent, but must be restricted to patients without haemorrhage. It should be used after anticoagulation therapy alone has not provided sufficient clinical improvement, and after ruling out other causes of a patient’s worsening condition.

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References

A elderly lady with collapse

I enjoyed reading the anatomical discussion about the third cranial nerve presented by Huwuez et al in a recent issue of the journal, and I wish to make a few relevant anatomical and clinical points.

All the extracocular muscles are innervated by an ipsilaterally located subnucleus, with the exception of the superior rectus muscle, which is innervated by a contralateral subnucleus.

The particular relationship between the third cranial nerve and posterior cerebral artery (above), the superior cerebellar artery (below), and the posterior communicating artery (parallel) deserve further comments, especially when clinicians are faced by an acquired isolated third nerve palsy in adults. As the pupillary fibres in the third cranial nerve are located dually and peripherally, a dilated pupil is frequently an early sign of a compressive lesion. An aneurysm at the junction of the posterior communication artery and internal carotid artery is a common cause. Actually, around 36% of all third nerve palsies are caused by aneurysms, especially posterior communicating aneurysms.

Other causes include compression or infiltration by neoplasms, infections, large dolicho-ectatic vessels, or shifted supratentorial structures. Occasionally it may be seen in generalised polynuropathy (Miller-Fisher variant).

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References

Failure to develop diabetic ketoacidosis in a newly presenting type 1 diabetic patient

In a recent issue of the journal McNulty and Hardy published a very interesting case history on the failure to develop diabetic ketoacidosis in a newly presenting type 1 diabetic patient. Their third self assessment question was “Why may this patient not have developed diabetic ketoacidosis?” The authors’ explanation is “because her insulinopenia was offset by her hypoadrenalism”. However, in patients with diabetic hyperglycaemic hyperosmolar syndrome (without ketoacidosis, as in the authors’ patient) increased concentrations of adrenal hormones are usually found. This makes the authors’ explanation very improbable. On the other hand, Schade and Eaton pointed out in 1977 (their p 596) that “insulin deficiency per se may not alone be a cause ketoacidosis”. An illustration of this problem is in the paper by Bouver et al: they compared two groups of diabetic patients, with lower and higher hyperglycaemia. Ketoene bodies were higher in the group with lower blood glucose. In decompensated diabetes mellitus, increased amounts of 34 organic acids have been identified; it is not known whether they are insulin dependent or not. Nevertheless, they can cause severe acidosis, for example, a blood pH of 6.85 was found in the patient of Vernon and Postellon in absence of acetocetic and β-hydroxybutyric acids.

Therefore, the authors should also ask: What are the exact mechanisms and details of development of both ketoacidosis and acido- sis without ketone bodies in diabetic patients?

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References
book provides a fascinating trip through history, following our understanding of this intriguing condition through to the present state of knowledge. It is recommended to anyone with an interest in the history of medicine and of epilepsy in particular.

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Professional Updating in Epidemiology. Design of Vaccination Programmes: From Sero-Epidemiology to Cost-Effectiveness
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