EDITOR’S CHOICE

Slimy uptake of an anti-convulsant

We all use Valproate. We use it to treat epilepsy (partial and generalised), bipolar disorder and migraine, making valproate one of the most highly prescribed medications in the neurology clinic. Its use as a potential treatment for seizures was discovered almost 40 years ago, having been used as an organic solvent for the previous 80 years. Within 4 years, valproate had become an approved (and highly effective) treatment. Moreover, we know that for many idiopathic primary generalised epilepsies, valproate is the treatment of choice with dramatic effectiveness. Despite this widespread familiarity, how many readers would be able to explain how valproate enters cells and its precise mechanism of action?

To help us, we need to turn to a recent article by Terbach et al. in the Journal of Cell Science. Knowing that the method of valproate uptake into cells was unknown, Terbach et al. set out to identify the mechanism by first studying valproate uptake in the slime mould, Dictyostelium. By carefully using a number of basic biochemical techniques, Terbach et al. were able to establish that valproate was actively taken up into cells against an electrochemical gradient, was protein-mediated and depended on a proton gradient. The researchers then used a mutant Dictyostelium screen to look for resistance to the growth-inhibitory actions of valproate. By using this approach, the membrane bicarbonate transporter, Slc4, was proposed as the membrane protein involved in active valproate uptake. Further experiments showed that by inhibiting this transporter with known specific pharmacological agents, valproate uptake was blocked. The mode of valproate uptake was conserved in zebrafish (Danio rerio) and Xenopus, and biochemical manipulation was shown to prevent valproate-induced developmental defects. Furthermore, the Slc4 family of bicarbonate transporters are also found in mammalian cells and are homologous to Dictyostelium Slc4 and have been implicated in fatty acid transport across membranes.

Is this clinically relevant? The valproate concentration in rat brain required to exert an anticonvulsant effect is around 0.1% of the necessary serum concentration. This relatively high serum concentration is required due to the low permeability of the blood-brain barrier to the drug. In addition to its valuable therapeutic properties, we are all aware of valproate’s adverse effects in patients, including teratogenicity and that this is likely to be serum dose-related. By identifying the uptake mechanism, this may be the first step in regulating the concentration of valproate in specific tissues leading to greater efficacy and minimising adverse effects. Key question remain, however, including those related to valproate’s precise mechanism of action.

This work demonstrates again the importance of laboratory-based experiments using basic biological models to answer key questions. It is a good example of ‘translational research’, whichever way the term is defined.

– Dr Rhys Roberts, Honorary Consultant Neurologist, Addenbrooke’s Hospital, Cambridge.

Long-term outcome in Parkinson’s patients with DBS

There are several studies describing the long-term outcome of idiopathic Parkinson’s disease e.g. the Sydney Multicentre Study, CamPaIGN (a population-based epidemiological study in Cambridgeshire), and outcome of patients with deep brain stimulation (DBS). This study reports very long-term data (>30 years from disease onset) in IPD patients with subthalamic nucleus (STN) DBS. The aim of the study was to ascertain whether certain clinical factors (gender, phenotype i.e. tremor-dominant vs. akinetic rigid, and age at onset) influenced outcome (time to develop complications), but the study was small with only 19 patients (and no power calculations, with long-term data available from 14 patients). The study did not compare DBS patients with control IPD patients. The cohort was slightly different to others studied (e.g. the Sydney cohort) in that the patients were very young (mean age 38.63 years). The authors found a progressive worsening of motor symptoms in both medication and stimulation ON conditions, and cognition. The majority of patients developed non-motor (non-levodopa responsive) symptoms, the hallmark of advanced IPD, at long term follow up. The percentage of patients developing these symptoms was lower than other similar studies perhaps because of the younger age at onset in this cohort and possible inclusion of genetic cases. It is known that younger patients have slower disease progression but tend to reach the same advanced-IPD milestones at the same age as older onset patients, with most patients in their 70s having such complications. Thus if this cohort had been followed up for even longer, the rates of complications may have been higher. Perhaps surprisingly, younger tremor-dominant patients while less likely to develop freezing of gait did not differ in the development of falls, postural instability, dysphagia, autonomic symptoms and dementia (although this may be a reflection of the small number of patients studied). Thus, this study adds to the literature on IPD outcome, with the main contribution being length of follow-up, but it does have some limitations.

– Dr Wendy Phillips, Consultant Neurologist, Addenbrooke’s Hospital and Princess Alexandra Hospital, Harlow.


The Wisdom of Age?

“The frail elderly are our market” was the rather arresting statement that I retained from another fruitless meeting with our local health commissioners. The needs of younger adults with complex disability tend to be addressed very much according to where one happens to live rather than one’s needs. Many specialist rehabilitation services apply upper age limits in a sometimes seemingly arbitrary fashion that effectively implies that older individuals with complex needs may not gain as much benefit from labour-
intensive multi-disciplinary rehabilitation as their younger counterparts. Is there any evidence for this assumption? As individuals with chronic neurological disease live longer, what will this mean for those of us charged with meeting their health needs? One would assume, rather bleakly, that increasing age coupled with physical or psychological disability could only mean an even greater demand for already scarce resources in the future. This Canadian study, however, would suggest not. The health service utilisation levels of a large retrospective cohort (part of the National Population Health Survey) in terms of GP attendances, specialist review, hospital admissions and home care services were assessed to evaluate the relative and combined effects of increasing age and disability. There were two competing hypotheses up for grabs; “double jeopardy” (age and disability will have a synergistic effect producing greater utilisation of health resources) and “age-as-leveler” (the social disadvantages of disability will be less important with increasing age leading to utilisation of health resources that would be less than the sum of the effects of age and disability). A number of other factors were used to create a multivariate model including demographic variables, individual impairments and activity levels.

Unfortunately, as the study was retrospective, the measures of “disability” were fairly crude self-reported items. The objective value of defining this cohort is, therefore, somewhat limited. Nevertheless, disability was found to be a much stronger predictor of health service utilisation than age. The surprising finding that age and disability seem to cancel one another out as predictors of health care utilisation with increasing age suggests that the “age-as-leveler” hypothesis is more viable than the “double jeopardy” hypothesis. Of course, there are any number of potential explanations behind this, but the suggestion that the health needs of younger adults with complex disabilities may actually diminish with increasing age is intriguing and worthy of further exploration.

-- Dr Lloyd Bradley, Consultant in Rehabilitation Medicine, Western Sussex Hospitals.


MuSK myasthenia - clinical characteristics and response to treatment

MuSK antibodies are comparatively rare, which are present in about 5-8% of all myasthenia patients (i.e. in approximately 50% of patients negative for the standard AChR-antibodies). It has been known that this is a predominantly oculo-bulbar condition with relative resistance to treatment using cholinesterase inhibitors or immunosuppression. In the current issue of Muscle and Nerve, Drs Evoli (Rome, Italy) and Sanders (Duke, NC, USA) publish the largest cohort study to date, on this group of myasthenia. Data from two independent, large and well-characterised groups of patients studied in two well-respected myasthenia centres looked at 110 patients (70 from Rome, 40 from Duke) followed up for an average of 11 years (Rome) and 5.3 years (Duke) (range, 0.5 to 33 years). Data from all MG patients (n=919) seen at Duke University and from a pooled group of 1582 AChR-antibody positive patients were used as comparative cohorts. Duke University had almost an equal proportion of African-Americans and Caucasians, whereas all patients from Rome were Caucasians.

The incidence of MuSK antibodies in AChR-antibody negative patients ranged from 39-49%, confirming earlier reports. 85% of MuSK patients were females and the mean symptom onset was in the fourth decade (range 64-68 years), at least a decade later than in the AChR-positive patients. Pure ocular presentation at onset was comparatively less common in the MuSK patients (36%) compared to all myasthenics (60%). Moreover, the vast majority of MuSK patients with initial ocular symptoms developed generalised disease between 2-3 weeks of onset. However, there was significantly more number of patients with MuSK myasthenia who had bulbar/neck symptoms or respiratory failure at initial presentation (50% vs 21%).

Repetitive nerve stimulation was abnormal in only approximately 60% of patients as compared to the 97% of patients who had increased jitter in at least one muscle on SFEMG. SFEMG was more likely to be abnormal in the facial muscles (>90%) compared to peripheral limb muscles (<50%). Only 57% patients improved on treatment with cholinesterase inhibitors which were more prone to produce side-effects (fasciculations, cramps, worsening of myasthenia etc). Plasma exchange was more likely to achieve clinical improvement compared to IVIg (59% vs 61%). Even though most MuSK patients had an acute onset, rapid progression and brittle course early in the disease, the long-term outcome was comparable to the AChR-antibody positive group with remission or improvement occurring in nearly 90% of patients in both groups with appropriate therapy.

In summary, this large study confirms the initial reports that MuSK myasthenia occurs predominantly in females, have frequent early crises and responds poorly to pyridostigmine. Facial muscle SFEMG performed by experienced neurophysiologists remains the most sensitive diagnostic test. Reassuringly, long-term prognosis is comparable, although multiple immunosuppressants may be required.

-- Dr Saiju Jacob, Consultant Neurologist, Queen Elizabeth Neurosciences Centre, Edgbaston, Birmingham.