LETTERS TO THE EDITOR

Reduction of plasma concentrations of large neutral amino acids in patients with maple syrup urine disease during crises

EDITOR.—Neurological dysfunction is a major clinical feature of children with maple syrup urine disease (MSUD). However, the mechanisms underlying the neuropathology of the disorder are poorly known. There is some evidence associating the appearance of the neurological symptoms with increased plasma concentrations of leucine or its ketcacid, or ketoisocaproic acid or both. Impairment of brain energy production by inhibition of key mitochondrial enzymes by the acidic metabolites that accumulate in this disease has also been reported. Although the reduction of branched chain amino acids and branched chain keto acids has been the main target for treatment of MSUD patients, a notable number of well treated patients have variable degrees of developmental delay accompanied by dysmyelination.

We performed a longitudinal study measuring glucose, insulin, and amino acid concentrations in plasma of eight children with MSUD aged 1 month to 7 years admitted to hospital during decompensation episodes, with convulsions, hypotonia, coma, ketonaemia/ketonuria, and metabolic acidosis, as well as after clinical recovery. Plasma from 10 age matched children showing no evidence of metabolic disease were analysed as controls. We found significantly reduced concentrations of various large neutral amino acids (LNAA), namely phenylalanine (5% of controls), tryptophan (13% of controls), methionine (18% of controls), and tyrosine (54% of controls) during decompensation, compared with the controls, apart from the expected increases of the branched chain amino acids leucine (28-fold), isoleucine (fourfold), and valine (threelfold). After recovery, the plasma concentrations of all amino acids returned to nearly normal concentrations. Insulin concentrations were significantly lower in the MSUD patients during crises, whereas glucose concentrations were slightly but not significantly decreased.

Therefore, the results rule out a possible stimulatory effect of insulin on the amino acid uptake by peripheral tissues. Another explanation for the decrease of plasma LNAA could be sequestration of the amino acids by peripheral tissues through LNAA competition with leucine for the efflux from these tissues, as observed in experimental hyperphenylalaninaemia. Considering that for the essential amino acids, brain concentrations are determined in large part by plasma concentrations and transport across the blood–brain barrier, our data might suggest that the decreased concentrations of LNAA in plasma of MSUD patients during decompensation may impair neurotransmitter and protein biosynthesis in the brain, further contributing to the neurological dysfunction characteristic of these patients. In particular, it is possible that patients with MSUD might benefit by supplementing their diets with LNAA.

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Management of tuberculosis in Wales: 1986–92

EDITOR.—We read with interest the recent paper on the management of tuberculosis in Wales. Almost a decade later, similar concerns led to a specialist paediatric TB service being established in 1995 at the Royal Hospital for Sick Children in Glasgow (RHSC). Key components have been the involvement of a few experienced staff, close liaison with community TB liaison health visitors, a computerised information management system, and the development of local guidelines based on those recommended by the British Thoracic Society (BTS). A recent audit was conducted. The results provide an interesting comparison to that published from Wales (table 1).

The two patient groups are very similar. Many of the deficiencies highlighted in the Welsh audit have been addressed, at least partially, within the context of a specialist paediatric service. Documentation and notification of cases were better. Bacteriological confirmation of tuberculosis was attempted in virtually all of our patients and achieved in 35% of children, comparing favourably with both the Welsh audit and a recent study from South Africa. More children treated at the specialist clinic received and completed appropriate treatment, as specified in the BTS guideline.

We believe that some of the advantages of the specialist paediatric TB service are worth highlighting and could be adapted to more general settings:

- The BTS guidelines emphasise that TB in children should be managed between thoracic physicians and paediatricians. TB liaison nurses with direct access to the clinical staff are a vital link allowing good communication between the two services.
- A specialist service with agreed protocols encourages uniformity of treatment. It enables expertise to develop and provides excellent training for both medical and nursing staff.
- A multidisciplinary approach enables non-compliance and poor clinic attendance to be rapidly addressed. Directly observed treatment can be implemented quickly if necessary.
- A computerised management system encourages better documentation. It also facilitates audit and research, and most importantly tight quality control.

The Welsh study showed that very few children were managed appropriately. The specialist service in our hospital has successfully attempted to improve this. However, such a service is not a panacea. With rising numbers of adults with TB, continuing vigilance among paediatricians is essential. The new paediatric TB guidelines will be an important step but continued audit and monitoring will remain vital.

D L CORRIGAN
Specialist Registrar,
R M BLAND
Senior Registrar,

Table 1 Audit of tuberculosis by the Royal Hospital for Sick Children in Glasgow compared with the Welsh audit

<table>
<thead>
<tr>
<th></th>
<th>RHSC Audit 1995–98</th>
<th>Wales Audit 1986–92</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of children</td>
<td>43</td>
<td>48</td>
</tr>
<tr>
<td>TB disease (n)</td>
<td>44</td>
<td>40</td>
</tr>
<tr>
<td>TB infection* (n)</td>
<td>29</td>
<td>10</td>
</tr>
<tr>
<td>Referred via contact tracing</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Demographics†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 4 years old</td>
<td>44</td>
<td>40</td>
</tr>
<tr>
<td>5–9 years old</td>
<td>40</td>
<td>38</td>
</tr>
<tr>
<td>10–14 years old</td>
<td>16</td>
<td>23</td>
</tr>
<tr>
<td>Male</td>
<td>49</td>
<td>60</td>
</tr>
<tr>
<td>Non-caucasian</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>Site of disease‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>91</td>
<td>65</td>
</tr>
<tr>
<td>Menigitis</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Bone</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Microbiological confirmation†</td>
<td>7</td>
<td>50</td>
</tr>
<tr>
<td>Not attempted</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Culture/microscopy positive</td>
<td>35</td>
<td>17</td>
</tr>
<tr>
<td>Tuberculin test†</td>
<td>Test done 100</td>
<td>95</td>
</tr>
<tr>
<td>88 Mantoux</td>
<td>37 Mantoux</td>
<td></td>
</tr>
<tr>
<td>63 Heaf</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCG status†</td>
<td>Had BCG 26</td>
<td>13</td>
</tr>
<tr>
<td>Not recorded</td>
<td>None</td>
<td>25</td>
</tr>
<tr>
<td>Notified to Public Health†</td>
<td>84</td>
<td>65</td>
</tr>
<tr>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment completed†</td>
<td>88</td>
<td>80</td>
</tr>
<tr>
<td>2 lost to follow up</td>
<td>10 lost to follow up</td>
<td></td>
</tr>
<tr>
<td>3 moved away</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are percentages unless otherwise stated.

*TB infection includes all children who received chemoprophylaxis.
†Children with TB disease only.
The vitamin K debacle

Editor,—I would like to raise two points about the editorial by Tripp and McNinch. First, they quote the incidence of vitamin K deficiency bleeding among babies given no prophylaxis as 10/1000 live births, citing the findings of the 1991 British Paediatric Surveillance Unit study. Table III of that paper quoted a “derived rate” for haemorrhagic disease of the newborn of > 8.63/100 000 newborn infants, or approximately 0.1/1000. Admittedly the possibility of underreporting makes this a minimum estimate, but it does not approach 10/1000. Was this an error, or have I misunderstood?

The second point relates to the sentence: “Breast feeding mothers are already advised to provide supplements of vitamins A, B, C, and D for their infants from the age of two months.” This is not supported by any citation and I am not aware of its origin. Recommendation 10 of the Department of Health’s publication Weaning and the weaning diet states “Breast fed infants under six months do not need vitamin supplementation provided the mother had an adequate vitamin status during pregnancy”. Supplementary vitamins A and D are recommended thereafter, and I know no evidence to support the routine use of vitamins B and C if the weaning diet is adequate.

Finally, I find it puzzling to argue that giving 25 µg phytomenadione daily must be safe purely because it is the dose in an infant formulation of vitamin K. The child is treated with no harm”.

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Guidelines for managing acute gastroenteritis

Editor,—In his otherwise excellent systematic review of the management of acute gastroenteritis, Murphy has overlooked the consensus about the assessment and management of dehydration that forms the basis of the World Health Organisation’s programme for the case management of diarrhoea contained within the guidelines for the newly developed Integrated Management of Childhood Illness (IMCI) strategy. The IMCI strategy contains similar but simplified recommendations to those contained in Murphy’s systematic review, and are produced primarily for use by health workers in developing countries. However, hospital based paediatricians need to be conversant with this strategy to be able to train and supervise health workers in its use. My personal experience of managing diarrhoea cases in the UK indicates that the IMCI diarrhoea case management guidelines are equally applicable in developed countries.

The IMCI guidelines first seek to classify the child with diarrhoea into three categories: acute diarrhoea, persistent diarrhoea, and dysentery. The degree of dehydration is then assessed according the presence or absence of four clinical signs: neurological condition, sunken eyes, delayed thirst, and skin turgor, and classified as being “severe”, “some”, or “no” dehydration. The child is treated according to the degree of dehydration.

Children with diarrhoea but no signs of dehydration are treated according to plan A—home base treatment with extra fluids including oral rehydration solution or home based fluids and continued feeding; those with some dehydration according to plan B—supervised oral rehydration over four hours with calculated volumes of oral rehydration solution in a health care facility; those with severe dehydration according to plan C—intravenous rehydration with Ringer’s lactate. These instructions are contained in WHO diarrhoea case management charts with their characteristic three colour triage design, which are commonly found in health facilities throughout the developing world. These clinical guidelines provide an effective framework for improved diarrhoea case management leading to reduced mortality from one of the major causes of child death worldwide.

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Guidelines for managing acute gastroenteritis

Editor,—Murphy’s paper “intended to provide evidence based recommendations about ... clinical management of infants and children with acute gastroenteritis”. Based on six references he concludes that “Many studies have now indicated that there is no advantage . . . . of . . . gradually increasing the feed concentration during the recovery phase after gastroenteritis.” Unfortunately one of these references concluded differently; another compared refeeding with no refeeding; and a third dealt with the issue of refeeding with and without cows’ milk. Therefore, three of the six references are unsuitable for his purposes. In the remaining papers, all patients were started on oral feeds after a classic but currently unattainable prolonged period (1 to 2.8 days) of starvation. One of them showed that, during the first 24 hours, vomiting was less frequent in the “regrading” group (P<0.04 v 1/12, p=0.02, Fisher exact test). None of these studies compared immediate with gradually increased feed concentration after a short period (4–6 hour) of rehydration as recommended by the European Society of Pediatric Gastroenterology and Nutrition.

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Dr Murphy comments:

The practice of increasing feed concentration stepwise (regrading) following an episode of acute gastroenteritis is in effect one of withholding nutrition. The burden of proof therefore lies with those who would refute the benefits of such regimens. I am grateful to Dr da Mota for pointing out the error in quoting the study by Placzk and Walker-Smith, which did indeed find some evidence in support of regrading. The remaining five studies were inappropriate. Although not all were controlled trials of regrading, they did “indicate” that there was unlikely to be an advantage to this practice. Each examined the outcome with a feeding regimen that either restricted or regraded feeds in the early phase of recovery, and generally little advantage was seen. By implication, if not direct evidence, regrading does not seem to be a strategy likely to be of benefit. Although Rees and Brook reported on a smaller scale, and our trials of regrading, they did “indicate” that there was unlikely to be an advantage to this practice. Each examined the outcome with a feeding regimen that either restricted or regraded feeds in the early phase of recovery, and generally little advantage was seen. By implication, if not direct evidence, regrading does not seem to be a strategy likely to be of benefit. Although Rees and Brook reported on a smaller scale, and our trials of regrading, they did “indicate” that there was unlikely to be an advantage to this practice.
a neonatologist using a Toshiba 140 with color Doppler. There is ready access to the machine and it is used liberally to monitor sick babies, not merely to exclude defects.

In two years, 537 echocardiographies were performed of which 233 were considered normal. A range of structural and dynamic defects was found, many of which were not suspected clinically—for example, three cases of fungal endocarditis and many patent ductus. No major defects appeared to have been missed, apart from a sinus venosus atrial defect, which was later diagnosed in a child who had chronic lung disease. Review of the early tapes did not disclose the lesion. No postmortem examinations have contradicted echocardiographic findings.

There are many advantages to this system: unnecessary transportations have been avoided, and others have been undertaken more wisely; cardiologists in Brisbane have been able to provide "arms length" care, until their scheduled visits; cardiac function and response to medication have been better monitored; research has been facilitated. Following research on the projection of fetal ultrasound images by videolink we are exploring its use in cardiology. It does work (at least at a band width of 384 kbps), however, the time involved in organising the consultation, the costs, and the difficulty in getting all the paraphernalia around a ventilated baby, render it very difficult for routine use. Ultimately, the neonatologist must be able to make some independent decisions, and therefore training is fundamental. Nevertheless, for us, the advantages of having a neonatologist familiar with echocardiography are such that it is difficult to imagine how we would otherwise function.

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3 Chan FY, Whitehill JS, Hayes L, et al. Real time foetal ultrasound consultation by telemedicine: what are the minimum requirements? J Telemed Telecare. [In press.]

Empyema thoracis: a role for open thoracotomy and decortication

Editor,—We were disappointed that Carey et al's recent article on surgical management of empyema thoracis was not balanced by a commentary providing the contrary view that surgery is rarely, if ever, needed in the modern management of empyema. Carey et al described the outcome of 18 children with empyema treated by open thoracotomy and decortication. The outcome in all 18 was good, with a mean length of stay in hospital after surgery of four days. They rightly emphasise that this treatment needed to be carried out in a regional cardiothoracic centre with experienced paediatric anaesthetists and surgeons and a paediatric intensive care unit, where several of the "younger" patients in this study might still intubated. This treatment is then not readily available to most children who develop empyema.

We agree that, in expert hands, surgery can be an excellent treatment for empyema, however, we do not believe that this report advances the current management of this condition. The authors make no attempt to compare open surgery with other treatments, such as closed drainage and fibrinolysis (with urokinase or streptokinase), and admit that there are no controlled trials of different management approaches for empyema. Therefore there are no data, either in their paper or in the available literature, to support their conclusion that "even in ideal cases, neither fibrinolysis nor thorascopic adhesiolysis can achieve more rapid resolution at lower risk [than open surgery]."

Our experience of closed drainage (pigtail catheter) and urokinase treatment given 12 hourly for three days in 18 children referred to our centre with empyema (n = 27 over two years; 20 with loculated empyema on ultrasound) is that it results in rapid resolution of fever and early discharge, with a mean length of stay of five days. Since we have been using urokinase, none of the children treated has required surgery. The choice therefore would appear to be between a general anaesthetic, an operation, a possible intensive care unit stay, and a scar (urokinase or saline in the management of empyema). One of the end points in this study is a requirement for surgery due to failure of resolution of symptoms. We encourage paediatricians looking after children with empyema to consider entering the study.

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Dr Carey comments:

Lack of facilities cannot be used as an argument against surgical treatment. Referral to facilities with the required expertise is possible throughout the United Kingdom. Surgeons and anaesthetists should not undertake occasional paediatric practice.1

We stand by our statement that there is no evidence to show that fibrinolysis or thoracoscopic adhesiolysis can achieve a better or safer outcome than that presented in our surgical series of stage II and stage III empyema. As we have already stated, alternatives to surgical series of stage II and stage III empyema. The outcome in all 18 was good, with a mean length of stay in hospital after surgery of four days. They rightly emphasise that this treatment needed to be carried out in a regional cardiothoracic centre with experienced paediatric anaesthetists and surgeons and a paediatric intensive care unit, where several of the "younger" patients in this study might still intubated. This treatment is then not readily available to most children who develop empyema.

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We stand by our statement that there is no evidence to show that fibrinolysis or thoracoscopic adhesiolysis can achieve a better or safer outcome than that presented in our surgical series of stage II and stage III empyema. As we have already stated, alternatives to surgical treatment with erythromycin may lead to toxicity and therefore are not recommended.8

Furthermore, it has been postulated that C. pneumoniae respiratory infection is one of the important causes of asthma attacks, not only in adults8 but also in children.9 Considering these reports and our results, we conclude that C. pneumoniae infection is strongly associated with respiratory tract illnesses from pharyngitis to pneumonia.9 Furthermore, it has been postulated that C. pneumoniae respiratory infection is one of the important causes of asthma attacks, not only in adults8 but also in children.9 Considering these reports and our results, we conclude that C. pneumoniae infection is strongly associated with respiratory tract illnesses from pharyngitis to pneumonia.9
Chronic cough: is it asthma?

EDITOR,—Faniran et al used a parental questionnaire to show that atopy was no more common in children aged 6–12 years with chronic cough than in “asymptomatic” children, whereas significantly more children with a history of wheeze showed evidence of atopy by skin testing. Children who wheezed at any time during the previous 12 months were designated to the “recent wheeze” group but chronic cough was defined as an episode of cough lasting more than three weeks, excluding those whose cough was associated with a cold or flu.

In asthmatic patients, wheeze is commonly associated with viral upper respiratory tract infection. If recurrent cough were to be considered as a mild variant of asthma then children who cough without wheeze after viral infection would be considered as asymptomatic in this study. Faniran et al’s findings are at a variance with a clinical study of children younger than 6 years referred to a district general hospital because of either chronic or recurrent cough or wheeze. We found evidence of atopy by skin testing in 63% of those with cough compared with 75% of children referred with both cough and wheeze, and only 10% of children without respiratory symptoms. Two years after presentation 25% of those with cough alone reported at least one episode of wheeze but most showed improvement in respiratory symptoms.

The history of cough or wheeze is subjective and varies with time. For each patient a careful clinical appraisal may indicate various causes, such as viral upper or lower respiratory infection, upper airway obstruction or habitual cough. If the pattern of presentation of cough alone resembles asthma and the child is too young to cooperate with lung function tests then a trial of asthma treatment with inhaled bronchodilators or even inhaled corticosteroids should be considered.

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Risks and benefits of cisapride

EDITOR,—Following the recent warnings against the use of cisapride in children from the Medicines Control Agency and the Committee on Safety of Medicines (CSM),1 we felt that the recent annotation by Lander and Desai2 was unwise. While it is right to question advice from the CSM, we feel it is more appropriate to do this in a personal practice article, and accompany it with a commentary.

Lander dismisses concerns about cisapride by saying they have not seen abnormalities of QTc in their series of 17 patients, as well as by quoting a study in which only two of 35 patients developed life-threatening arrhythmias.3 These studies are small and statistically unsound, but they do show us an unacceptably high risk when using cisapride; one of our patients suffered sudden infant death one week after starting cisapride, an event we obviously reported to the CSM.

Lander and Desai also suggest measuring QTc before and after starting cisapride, but our recent experience of a regional neonatal unit surgical patient showed that not all doctors can measure QTc accurately, making this safeguard inadequate.

We agree there is evidence that cisapride reduces the incidence and severity of gastro-oesophageal reflux in some circumstances. However, we also agree with the CSM, which advises that it is unsafe to prescribe a drug with the potential side effect of sudden death when there are alternatives. We are concerned that this second, safer point of view, even if published as a letter, will have less impact than an annotation.

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1 CSM/MCA. Pharmacovigilance 1998;24 (August).

Dr Faniran et al comment:
As opposed to Dr Lewis’s comments, atopy was measured skin prick test in all the 1245 children included in our study and not only in children with wheeze. We found that children with persistent cough had less morbidity and less atopy compared with children with wheeze. This finding is in agreement with other epidemiological studies4 in contrast to the hospital based studies referred to by Dr Lewis.5 As stated in our paper, we believe clinic attenders with persistent cough are unlikely to be representative of children in the community with this syndrome and may have symptoms with a different cause. As such, it might be inappropriate to treat children in the community with persistent cough as asthmatic. Rather, it is important to carry out studies to determine the appropriate treatment for these children.


Dr Lander comments:
We raised two issues: first, the CSM claimed insufficient data supported the use of cisapride in children younger than 12 years.1 Our review did not support this so we asked the CSM to clarify their reasoning; second, the CSM contraindicated cisapride in infants <36 weeks’ gestation for 3 months after birth. We did not advocate against this contraindication but questioned the evidence for it. We believe that in a correct dose and avoiding interfering drugs, cisapride may be safe and useful, it would be wrong to contraindicate it without good evidence.

Although we abide by the CSM’s contraindication, many neonatologists still use cisapride in preterm infants. Ward et al found cisapride use in infants <36 weeks’ gestation and <3 months of age to be widespread in the USA.2 Adverse events occurred only with very high doses or in combination with drugs inhibiting cisapride metabolism. Arrhythmias were reported in fewer than 1/11 000 treated premature babies, further encouraging us to think that the issue of prematurity should be revisited by the CSM.

Jones and Wagstaff are right that QTc is not simple to measure and it varies between leads. We have looked at the QTc estimated in different leads of a given ECG. The difference between the largest and smallest QTc in a given ECG is the QTc dispersion. The values of QTc dispersion show intraobserver and interobserver variation, making analysis difficult; however, the mean QTc across a number of leads does not appear to rise significantly on cisapride but the dispersion decreases. Cisapride seems to raise the shortest QTc more than the longest.

In clinical practice, a simple estimate of QTc should establish whether a child has a pathologically prolonged QT interval, indicating that cisapride should be avoided.

1 CSM/MCA. Pharmacovigilance 1998;24 (August).
Reduction of plasma concentrations of large neutral amino acids in patients with maple syrup urine disease during crises

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