LETTERS TO THE EDITOR

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Fludarabine in the treatment of an active phase of a familial haemophagocytic lymphohistiocytosis

Editor,—Familial haemophagocytic lymphohistiocytosis (FHL) is a lethal disease with an uncontrolled activation of T lymphocytes and macrophages due to a perforin gene defect.1 The current curative treatment is bone marrow transplantation. However, favourable outcome is associated with clinical remission status at the time of the procedure.2–5 Unfortunately, the use of steroids, etoposide (VP16), cyclosporin, and antithymocyte globulins alone or in association frequently fails to control recurrent active phases.

BL, a 2 month old boy, was admitted in June 1999 for an active phase of FHL. His elder brother had died of FHL. The diagnosis was established on clinical (vomiting, fever, pallor, hepatosplenomegaly) and biological features (pancytopenia, hypertriglyceridaemia (3.82 mmol/l), haemodilution, hypofibrinemia (0.65 g/l), a moderate elevation of aspartate transaminases (2N) and haemophagocytosis on bone marrow aspi- nation) of aspartate transaminases (2N) and haemophagocytosis on bone marrow aspiration. No central nervous system abnormality was observed on cerebrospinal fluid analysis and cerebral magnetic resonance imaging.

A first remission was obtained with the combination of steroids: prednisolone (2 mg/kg/day), VP16-phosphat (150 mg/kg/day, d1–d3), cyclosporin A (4 mg/kg/day, continuous infusion), and antithymocyte globulins (10 mg/kg/day, d1–d5) three weeks after diagnosis. Despite maintenance treatment, relapse occurred one month later with severe pancytopenia. No remission was obtained with a second course of steroids, VP16-phosphate, and antithymocyte globulins. Two and a half months (day 76) after diagnosis, a course of fludarabine (30 mg/m²/day for four days) was initiated and dramatically improved our patient’s condition regarding the clinical and all biological criteria of FHL. An additional course was given on day 92. Transient neutropenia and a noticeable lymphopenia were observed. After a busulfan (120 mg/m²/day for four days) and cyclophosphamide (30 mg/kg/day for four days) conditioning regimen one month after the last course of fludarabine, we performed a haematopoietic stem cell transplant with the father’s CD34+ HLA-half-identical peripheral cells (Miltenyi, Germany). Haematological reconstitution was observed from day 24 post transplant. There was transient grade II acute graft versus host disease (skin, liver). No relapse of FHL has occurred to this date (day 330 post transplant).

Treatment of active phases of FHL is based on drugs killing immune-competent cells. Fludarabine is a purine antimetabolite with a strong immunosuppressive action.6 During treatment with fludarabine for B cell malignancies, an important decrease in the T cell subpopulations, particularly of the natural killer phenotype (CD16/56+), was observed. Our patient’s response to the first course of this drug was dramatic and allowed bone marrow transplant when in good clinical condition. Nevertheless a series of patients is needed to assess the efficacy of fludarabine for the treatment of active phases of FHL.

We thank Dr JL Stephan for his helpful clinical advice.

Correspondence to: Prof JP Vannier (Jean-Pierre.vannier@chu-rouen.fr)

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
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<tr>
<td>Age at diagnosis (years)</td>
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<td>1.5</td>
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<tr>
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<tr>
<td>Interval from exposure to appearance of symptoms (months)</td>
<td>7</td>
<td>12</td>
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<tr>
<td>Interval between appearance of symptoms and diagnosis (weeks)</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Hepatomegaly (cm)</td>
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<tr>
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<td>WBC (&lt;10⁶/l)</td>
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<td>Platelets (&lt;10⁹/l)</td>
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<td>Triglycerides (mmol/l)</td>
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<tr>
<td>Serum IgG (g/l)</td>
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LDH = lactate dehydrogenase

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Visceral leishmaniasis: also beware of these deceptive microbes in non-endemic countries!

Editor,—We read with interest the report by Grech et al.7 From their population based study, it seems that the annual incidence of visceral leishmaniasis (VL) declined considerably in Malta as a result of the eradication of stray dogs. VL is still endemic around the Mediterranean Sea and sporadic cases are reported in children living in Northern Europe. It seems likely that with increasing tourism the incidence of VL will also increase in areas where until recently this condition would not even be thought of. During the last 18 months, we have diagnosed three children with VL. As the presentation features can be fairly dramatic and physicians in Northern Europe are not always alert to the possibility of this condition, we would like to call attention again to the possibility of VL in non-endemic countries.

The main clinical features of the patients are shown in table 1. All three children presented with spiking high fevers, anorexia, hepatosplenomegaly, and pancytopenia. The onset of the symptoms was insidious and it took 3–12 weeks to establish the diagnosis. In all three patients this was achieved through bone marrow aspiration and the demonstration of the typical amastigotes in macrophages. The diagnosis was further confirmed through the demonstration of antibodies to the leishmania parasite. All three patients needed erythrocyte transfusions and patient three also needed platelet transfusions. A 5–10 day course of liposomal amphotericin-B was given to all three children. The treatment was well tolerated, and they all became afebrile within a week. Pancytopenia subsided over the ensuing 2–3 weeks and the children gradually returned to normal activity.

 Naturally, we cannot draw epidemiological conclusions from such a small number of patients, but it is intriguing to find three unrelated cases within a relatively short period. While the eradication of stray dogs may go a long way to reduce the incidence of VL, vaccination would be more desirable.7 Although resistance and immunity against the leishmania parasites is not well understood, the seemingly increasing incidence of VL in children travelling from Northern Europe might be because they have no transplacental immunity against the parasite and are therefore more prone to develop this condition than local children. There is much in common between the presentation features of the haemophagocytic syndromes and VL. It is noteworthy that all three of our patients showed signs of macrophage activation and haemophagocytosis was observed in their bone marrow smears. With increased awareness of this condition by physicians in non-endemic countries, the time required to reach the correct diagnosis and institute treatment should be reduced.

During

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Intestinal inflammation in cystic fibrosis

EDITOR,—Following their studies of whole gut lavage fluid, Smyth et al have suggested that a non-idiothetic intestinal inflammation occurs constitutively in patients with cystic fibrosis (CF), as a consequence of a proinflammatory effect of the patient's CFTF mutations. They reported marginally elevated excretion of IgG, IgM, interleukin 1 (IL-1), neutrophil elastase, and eosinophil cationic protein, and much more significant increase in excretion of IL-8 and albumin, but no increase in excretion of α1 antitrypsin or IgA. In this study where lavage fluid was administered continuously, and intestinal effluent was collected in discrete samples, pooling of the effluent before analysis would have allowed small differences in calculated inflammatory marker outputs to be interpreted as representative of gastrointestinal output. Of all the inflammatory markers presented, only IL-8 shows a range of cytokine outputs in CF patients with or without fibroinflammatory colonopathy that did not extend into the range seen in controls, in these non-parametric datasets. The authors’ evidence for intestinal inflammation therefore relies heavily on the validity of their IL-8 Quanti- kine assay (R&D Minneapolis) protocol.

I have explored the validity of this assay for use in supernatants of fecal homogenates in children with cystic fibrosis and found it wanting. Recovery of a 500 pg/ml spike of IL-8 progressively increased from 41% in samples which were a 12-fold dilution of faeces to 189% in samples which were a 120 000-fold dilution of faeces, when used according to manufacturer’s instructions. Prediluting the samples 50/50 in newborn calf serum, and using calf serum for further dilutions gave this assay (R&D catalogue no D8000) mean (SD) spike recovery of 92.1 (12.5%) and coefficients of variation of 3.4% (intra-assay) and 6.85% (interassay). Without knowledge of the IL-8 ELISA validation data of Smyth et al, I assume that this assay returns similarly spuriously high IL-8 concentrations in polyethylene glycol based whole gut lavage fluid to my 120 000-fold dilution faecal supernatant. The absence of a significant difference between CF patients and controls in their α1 antitrypsin outputs suggests that intestinal inflammation was not present in the CF patients. Overestimation of the WCLF IL-8 concentration would explain the apparently implausibly large volumes of swallowed sputum that the authors estimate would be required to account for their results. In this study which could not turn off the mucociliary escalator, but did dramatically increase the rate of intestinal transit and excrete exogenous pancreatic enzymes, swallowed sputum is the most likely explanation for the results.

G BRAHMS
Paediatric Gastroenterology, West Suffolk Hospital, Haverhill, Suffolk


Intestinal inflammation in cystic fibrosis: an alternative hypothesis

EDITOR,—I was interested by the report of Smyth and colleagues on the finding of markers of intestinal inflammation in whole gut lavage in patients with cystic fibrosis. As the α1 antitrypsin levels were not elevated when compared to controls, perhaps another hypothesis needs to be considered. Conceivably the inflammatory markers are not increased within the bowel, but rather, they are not degraded due to the lack of intestinal enzymes, α1 antitrypsin, which is resistant to proteolytic enzyme activity, would not be affected by such a phenomenon and, therefore, would be the same in patients with cystic fibrosis and controls. Perhaps the authors would need to resort to the somewhat dated technique of radio labelled albumin to definitively answer this question.

L EISENBERG
18372 Clark St, Suite 216, Tarzana CA 91356, USA
email: leisenb@aol.com

Intestinal inflammation in cystic fibrosis

EDITOR,—We thank Dr Briars for his recent comments and are aware of his opinions regarding the potential source of the intestinal cytokines that we discussed in paper, including reference to his previous paper. We do not agree that our data is dependant upon IL-8 alone. We have shown statistically significant differences for a whole range of proteins and types of assays. Due to the large number of proteins and types of assays that we have performed, we have not carried out the extensive experiments for IL-8, as reported by Dr Briars. We do know that the polyethylene glycol, a key constituent of the lavage fluid, does not affect the IL-8 assay. There are two reasons why variable recovery is unlikely to be a major factor in our results. Firstly, by collecting whole gut lavage, any intestinal secretions present, including bile, remain. Substances found in faeces (for example, steroclobin) are effectively absent. Secondly, whole gut lavage is a perfusion system found to be equivalent to balloon perfusion systems. Thus, the dilution of any faecal IL-8 would be very similar between the subjects and controls. Using whole gut lavage minimises any interference from intestinal material as much as is feasible in vivo.

Assuming the worst case scenario from Dr Briars’ data (that is, a two fold overestimate of IL-8 in the cystic fibrosis patients, which is not found in the controls), this still shows significantly increased IL-8 output in cystic fibrosis patients (p<0.0001) and unfeasible volumes of sputum would still be required. For these, and reasons detailed in our paper and previous correspondence, we do not believe that sputum is the primary source of the abnormalities found. Our observations concerning the increase in intestinal inflammatory markers in the whole gut lavage of cystic fibrosis patients have now been supported by a study which investigates intestinal inflammation within mucosal biopsy samples. This provides additional support to the hypothesis that the basic defect of cystic fibrosis is transmembrane regulator protein.

Dr Eisenberg correctly points out the potential influence of pancreatic enzymes and degradation. The results we found for α1 antitrypsin were unexpected, given differences for albumin and IgG. Some discordance in data has been found previously in whole gut lavage from subjects with active inflammatory bowel disease who are pancreatic deficient and who also can have raised intestinal permeability.

However, our data that showed raised albumin and IgG are consistent with well established data showing raised intestinal permeability in children with cystic fibrosis. As discussed, it has been found that protein outputs from balloon perfusion experiments (which exclude upper intestinal secretions) are similar to those found in whole gut lavage, which suggests that any potential effect of degradation from pancreatic enzymes is minimal. We also showed eosinophilic cationic protein to be raised in children with cystic fibrosis. As with α1 antitrypsin, this is relatively stable in faeces at room temperature (24% 21% loss over 24 hours). This loss would be considerably lower during whole gut lavage. Thus, degradation would be unlikely to explain this difference.

N M CROFT
Department of Paediatric Gastroenterology, St Bartholomew’s and the Royal London School of Medicine and Dentistry, Queen Mary and Westfield College, London, UK

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Intestinal inflammation in cystic fibrosis


Dr Grech comments:

The development of visceral leishmaniasis after travel to endemic countries is not a new fac of this problem. At the time of writing, a Medline search using the key words visceral leishmaniasis and Malta yields 16 papers. Of these, almost a third (n=5) deal with patients who visited Malta and contracted the disease.

V GRECH
Paediatric Department, St Luke’s Hospital, Guardamangia, Malta


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V GRECH
Paediatric Department, St Luke’s Hospital, Guardamangia, Malta


Lumbar puncture should not be performed in meningococcal disease

EDITOR,—I was dismayed to see your publication of the letter by Dr Sam regarding the role of lumbar puncture in meningococcal disease. While fully understanding the need to get as much information as possible, the benefits of isolating the causative organism need to be weighed against the risk of causing clinical deterioration in a patient who may have carotid artery compromise and increased intracranial pressure, both of which are recognised contraindications to lumbar puncture. There are clear and recognised risks of performing such a procedure in such patients.

The potential benefits of lumbar puncture include making a diagnosis of meningitis and isolation of the organism for epidemiological and sensitivity testing. In the UK the typical haemorrhagic rash of meningococcal infection is pathognomonic of the disease and should be treated as such prospectively, until further confirmatory evidence is available. With polymerase chain reaction (PCR) of meningococcal DNA in blood allowing up to 100% sensitivity for diagnosis in the first 24 hours of illness, there is little to be gained from looking for bacteria or cells in the cerebrospinal fluid (CSF).

The antibiotic regimen is no different for either meningococcal meningitis or septicaemia, with seven days of a third generation cephalosporin being the treatment of choice because of improved CSF penetration. There are no reports of meningococcal resistance to this treatment in the UK, so performance of a lumbar puncture for bacterial sensitivity testing appears to be unnecessary.

Prospective therapy while awaiting results of culture or PCR from blood seems to be a small price to pay in this life threatening illness. An analogy could be drawn from the management of epiglottitis. It is generally accepted that throat swabs should not be taken from children with epiglottitis until the child’s airway has been protected, because of the risk of clinical deterioration. It is time that textbooks of emergency paediatrics stated clearly that lumbar punctures on children with a haemorrhagic rash, and clinical signs of meningococcal infection should not be carried out until the clinical condition has been stabilised, and only if the procedure will add further valuable information that cannot be obtained elsewhere.

SIMON NADEL
Consultant in Paediatric Intensive Care, St Mary’s Hospital, London, UK
snadel@ic.ac.uk

Table 1 Potential cost of prophylaxis in the community

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Hajj and risk of blood borne infections

EDITOR,—Annually, some two and a half million pilgrims congregate in the city of Mecca in Saudi Arabia to perform the Hajj (pilgrimage), a religious duty for all adult Muslims who are physically and financially able. Because of the very large numbers of peoples from disparate regions, and the hostile climate of the Arabian Desert, the chances of disease are high. Heat exhaustion, sunstroke, and infectious diseases such as pneumonia and meningitis have traditionally caused the greatest disease burden.1

One of the rites of the Hajj is for males to shave their heads, although trimming the hair is also acceptable. Most will choose the former, often in makeshift centres run by opportunistic barbers. A razor blade is commonly used, and may be used on several scalps before ultimately being discarded. The risks of blood borne infections such as hepatitis B and C are obvious, especially considering that many pilgrims come from regions of the world where such infections are endemic.2 Pilgrims should be aware of the potential dangers and be educated to insist on the use of a new blade. We would also strongly recommend that they be vaccinated against hepatitis B.

AR GATRAD
A SHEIKH
Manor Hospital, Main Road, Walsall WS2 9PS, UK

Table 1 Potential cost of prophylaxis in the community

<table>
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