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.


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

Editor,—We read with interest the report by Grech et al.

In three children travelling from Northern Europe they were able to reach the correct diagnosis and institute treatment again to the possibility of visceral leishmaniasis. Although resistance and immunity against the Leishmania parasite varies between patients, but it is intriguing to find three unrelated cases within a relatively short time.

While the eradication of stray dogs may go a long way to reduce the incidence of VL, vaccination would be more desirable.

Although resistance and immunity against the Leishmania parasite 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.

Table 1 Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (years)</td>
<td>1</td>
<td>1.5</td>
<td>2</td>
</tr>
<tr>
<td>Holiday destination where infected</td>
<td>South of France</td>
<td>Elba</td>
<td>South of Spain</td>
</tr>
<tr>
<td>Interval from exposure to appearance of symptoms (months)</td>
<td>7</td>
<td>12</td>
<td>6–18</td>
</tr>
<tr>
<td>Interval between appearance of symptoms and diagnosis (weeks)</td>
<td>6</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Hepatomegaly (%)</td>
<td>6</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Splenomegaly (%)</td>
<td>10</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>Hb (mmol/l)</td>
<td>2.9</td>
<td>3.0</td>
<td>15</td>
</tr>
<tr>
<td>WBC (x 10⁹/l)</td>
<td>4.5</td>
<td>3.0</td>
<td>15</td>
</tr>
<tr>
<td>Platelets (x 10¹²/l)</td>
<td>47</td>
<td>107</td>
<td>10</td>
</tr>
<tr>
<td>Ferritin (µg/l)</td>
<td>10813</td>
<td>260</td>
<td>4612</td>
</tr>
<tr>
<td>LDH (U/l)</td>
<td>4779</td>
<td>914</td>
<td>1761</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>5.64</td>
<td>6.9</td>
<td>3.9</td>
</tr>
<tr>
<td>Serum IgG (g/l)</td>
<td>13.9</td>
<td>15.6</td>
<td>36</td>
</tr>
</tbody>
</table>

LDH = lactate dehydrogenase

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Dr Grech comments:

The development of visceral leishmaniasis after travel to endemic countries is not a new facet 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. 1–5

V GRECH
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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-idiopathic intestinal inflammation occurs constitutively in patients with cystic fibrosis (CF), as a consequence of a proinflammatory effect of the patient’s CFTR mutations. 1 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 u antitrypsin or IgG. 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 cytokite outputs in CF patients with or without fibrosis. The authors' evidence for intestinal inflammation therefore relies heavily on the validity of their IL-8 Quanti-key assay (R&D Minneapolis) protocol.

I have explored the validity of this assay for use in supernatants of faecal 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 180% in samples which were a 120 000-fold dilution of faeces, when used according to manufacturer’s instructions. Thus, the dilution of any interfering factors 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’s 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 the 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, 1–2 we do not believe that sputum is the primary source of the inflammatory 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. 3 This provides additional support to the hypothesis that the basic defect of cystic fibrosis transmembrane regulator cannot be proinflammatory.

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References


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 inflammation in whole gut lavage fluid in patients with cystic fibrosis. 1 As the u 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. u 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.

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Intestinal inflammation in cystic fibrosis

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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 our paper, including reference to his previous paper. 1–2 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 assay and thus, the cystic fibrosis phenotype 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 used as 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, which are known to affect the IL-8 assay, 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, which are known to affect the IL-8 assay, does not affect the IL-8 assay.

Secondly, we do not believe that sputum is the primary source of the inflammatory 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. 3 This provides additional support to the hypothesis that the basic defect of cystic fibrosis transmembrane regulator cannot be proinflammatory. 3

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 4 who are pancreatic sufficient and who also can have raised intestinal permeability. 5

However, our data that showed raised albumin and IgG are consistent with well established data showing raised intestinal permeability in children with cystic fibrosis. 6 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 IgG may be due to methodological artefact. 3 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 (approx 21% loss over 24 hours). 7 This loss would be considerably lower during whole gut lavage. Thus, degradation would be unlikely to explain this difference.

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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 already be septic with uncontrolled intracranial pressure, both of which are recognized contraindications to lumbar puncture. There are clear and recognized performance indicators for this 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 meningitis, should not be carried out until the clinical condition has been stabilized, and only if the procedure will add further valuable information that cannot be obtained elsewhere.

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Prophylaxis for respiratory syncytial virus infection: missing the target

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doi: 10.1136/adc.84.4.373g

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