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Hereditary Angioneurotic Oedema — The Management of the Problem in a Family

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In a recent review in this Journal of the syndrome of hereditary angioneurotic oedema (HAO), some of the problems which may arise in patients affected by this condition were outlined (Abdullah and Greally, 1980).

The inherited defect in these patients resides in an incapacity to produce an inhibitor of the first component of complement, C1 esterase inhibitor (Cl INH). In the absence of this factor, other complement components undergo rapid turnover, particularly C4 and C2, the latter releasing subcomponents with kinin activity. Kinins have the effect of producing increased vascular permeability. Thus, in HAO, there is an exaggerated response in the early stages of the acute inflammatory process, i.e. that phase which involves increased vascular dilatation and oedema. Such a response is the essence of the syndrome of HAO and it is worth recalling that an attack may be precipitated by such diverse stresses as menstruation, dental extraction and emotional disturbance. In this article, we report on the approach taken in handling HAO which afflicted a family in several different ways.

The family under investigation is represented by Figure 1, showing the family tree. Clinical histories and subsequent serum analyses indicated that the affected individuals were two children (E.D. and P.D.) and their mother (J.D.). The family history also revealed that a maternal grand-aunt of the children had died in hospital at the age of 26, shortly after incision of a swollen lip which was thought to contain an abscess. Measurement of serum Cl INH was carried out on the mother and her three children.

In Figure 1: Family tree.

Methods
Immuno chemical quantitation was performed, using radial immunodiffusion (Mancini, 1965) and functional assay of Cl INH by the method of Levy and Lepow (1959). In addition, where sample size permitted, the complement components C4 and C5 were measured using radial immunodiffusion.

The results of these tests are seen in Table 1 and establish the deficiency of Cl INH in the mother (J.D.), daughter (E.D.) and infant son (P.D.).

Table 1
Results of Complement Assays on Family Members

<table>
<thead>
<tr>
<th>Family Member</th>
<th>Cl INH (Immunochemical)</th>
<th>Cl INH (Functional)</th>
<th>C3</th>
<th>C4</th>
<th>C5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother (J.D.)</td>
<td>4.0</td>
<td>0</td>
<td>122</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Daughter (E.D.)</td>
<td>0</td>
<td>0</td>
<td>135</td>
<td>6</td>
<td>8.8</td>
</tr>
<tr>
<td>Daughter (J.D.)</td>
<td>26</td>
<td>ND</td>
<td>139</td>
<td>12</td>
<td>9.5</td>
</tr>
<tr>
<td>Son (P.D.)</td>
<td>11.5</td>
<td>ND</td>
<td>149</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Normal Values</td>
<td>11-39 mg%</td>
<td>2.2-6.6 u/ml</td>
<td>100-190</td>
<td>14-51</td>
<td>9-21</td>
</tr>
</tbody>
</table>
Case Reports

The mother (J.D.), aged 34, first presented in August 1978 with a history of sudden onset of swelling of the lips, eyes, face and throat. The attack was preceded by a feeling of weakness and fatigue which lasted for several hours and accompanied by colicky abdominal pain, vomiting and diarrhoea. In childhood, she had been hospitalised on three occasions for similar attacks, which had recurred intermittently since. They had, however, become more frequent and at the time of presentation had been occurring once each week. She was skin tested against a wide range of allergens and was found to be negative to them all. Her initial treatment was with an anti-histamine which provided transient symptomatic relief during an attack. Shortly after first presenting, she became pregnant and in due course was delivered of a son. Her pregnancy was uneventful. In August 1979, she was first treated with Danazol 50 mgms thrice weekly after laboratory results indicated what the basic nature of her disease was. On this regimen, she suffered 5 attacks in one month and her dose was increased to 50 mgms daily. Interestingly, the attacks became more frequent but less severe so, after a further month, she was put on 100 mgms daily. She improved considerably and in the month that followed had but one attack. Her dose of Danazol was again increased until, by December 1979, she was symptom-free. Analysis of serum complement components was undertaken at intervals during the course of her therapy and the results are presented in Table 2.

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The daughter (E.D.) presented primarily because of pain in her teeth, several of which were impacted and one of which was carious. Serum complement studies indicated that she had no detectable C1 INH. Since dental extraction in these circumstances carries with it the risk of acute onset of angioedema which may affect the glottis, it is imperative that an adequate level of C1 INH be present in the patient's serum before such manipulations are undertaken. This patient was put on treatment with Stromba, a Danazol analogue, and C1 INH levels were monitored at regular intervals. In addition, as it became clear that C1 INH was being produced, tranexamic acid (Cyclokapron) was also given to the patient in order to conserve the inhibitor. Table 3 outlines the patient’s response to this treatment.

The son (P.D.) is showing some signs of facial swelling and is a little colicky. He has low levels of serum C1 INH and C4 but no treatment is indicated at present. The parents have been told that, as this is an autosomal dominant condition, there is a 50 per cent chance of it occurring in any future pregnancy.

Discussion

The family investigated here was problematical in several respects. The decision to treat the mother was based on increased frequency and severity of the attacks of angioedema. A potential problem of even greater magnitude existed in her daughter, who was...
faced with the risk of developing acute angioedema of the oropharynx and larynx due to dental surgery. The infant son has not yet manifest any symptoms of significance in spite of a low level of Cl INH, but will clearly require close surveillance in the years ahead.

While the immediate problems of mother and daughter have been alleviated with androgen derivatives, this form of treatment may have its drawbacks. Danazol may have virilizing effects when given over a long period of time and the mother did develop amenorrhoea at a dose of 200 mgms daily of this drug. It may be appropriate to use the same form of treatment on mother and daughter. Stromba has little androgenic activity but it remains to be seen whether it is as effective as Danazol in symptom alleviation in the mother. Therapy with Stromba and Cyclokapron is gradually being reduced in the daughter and will probably be suspended altogether. She grew rapidly on treatment but there is a possibility of premature fusion of the epiphyses.

Viewing the results of the complement assays, it is clear that symptomatic improvement was associated with an increase in Cl INH and C4 as measured by immunochemical methods. The functional assay used was not a good indicator of responsiveness to therapy and indicates that a different relationship exists between the results of these assays in patients with HAO and in normals (Abdullah and Greatly, unpublished observations). Practical considerations apart, the success of two different, albeit similar, androgen derivatives in promoting synthesis of Cl INH raises questions as to the specificity of effect of these drugs and the fundamental nature of HAO.

While inhibitor synthesis and its preservation are clearly important in alleviating symptoms, the endocrinological mechanism by which such synthesis is promoted is still not clear. Is there a direct effect on the liver cells by these drugs inducing them to synthesize Cl INH, or do they act as inhibitors of pituitary hormones, thus altering receptors on target cells in the liver and other tissues for other hormones to induce the effect observed? For the moment, these questions must remain speculative.

More recently, a different approach to the therapy of Cl INH deficiency has been documented (Gadek et al., 1980). Here, the missing factor Cl INH was given to patients suffering from attacks of angioedema and effectively prevented the attacks. The Cl INH used had the advantage of stability over a twelve-month period and could be self-administered also. This form of treatment is free of the potential complications of Danazol, and further clinical trials are awaited with interest.

References