Recurrent Attacks of Abdominal Pain and Fever With Familial Segmentation Arrest of Granulocytes

By J. Murros and A. Konttinen

In a family four sisters have suffered, the eldest two for nearly 20 yr, from recurring attacks of abdominal pain and fever of unknown etiology. Clinical similarity to familial Mediterranean fever is striking. However, they all have a segmentation arrest of granulocytes, which resembles the Pelger-Huet anomaly. It seems that the association is more than a mere coincidence.

INTRODUCTION

The clinical harmlessness of the Pelger-Huet anomaly has been established. The anomaly is characterized by arrested segmentation of granulocytes, typical appearance of the granulocytic nuclei, and autosomal dominant inheritance. The affected persons have no clinical complaints. Here we describe a family in which four sisters who have a segmentation arrest of granulocytes resembling the Pelger-Huet anomaly suffer from paroxysmal bouts of abdominal pain and fever. Despite extensive investigations no explanation has been found for the malady.

FAMILY HISTORY

The proposita (V. P.), a 32 yr old unmarried shop assistant, has since early childhood suffered from unexplained attacks of cramping abdominal pain with a rise in temperature. The attacks usually occur irregularly at intervals of 2-5 wk, but sometimes several months have elapsed without symptoms. The pain begins without prodrome in the epigastrium and radiates over the whole abdomen. Some days after the onset there is a rise in temperature, usually to over 38°C, which lasts 12-24 hr. Pain persists longer than pyrexia and the whole attack lasts 4-5 days. Between the attacks she has been in good health. There are no known provoking factors for the attacks nor any history of atopy, and the attacks do not coincide with the menstrual cycle, which is normal. During the attacks she has never had rash, arthralgia, bloody stools, or abnormalities in urine. Administration of various antibiotics has not been of any benefit. During cortisone treatment there was a temporary remission of symptoms, but after a few months, the symptoms were manifested again, and cortisone was stopped.

At the age of 10 she was admitted to hospital for the first time: an undefined infection was suspected, a large proportion of leukocytes were interpreted as stabs. At the age of 18 she had rheumatic fever and developed mitral and aortic regurgitation. Five years later she was affected by subacute bacterial endocarditis: Streptococcus viridans grew in blood cultures. Afterwards endocarditis was suspected several times during the periods of pain and fever, but blood cultures were always negative. In the course of years she also developed gallstones, but, after cholecystectomy, the pains have continued as previously. In the operation a small accessory spleen was found, but nothing else was abnormal.

Over the years she was admitted to hospital numerous times and examined repeatedly and exhaustively. Extensive x-ray examinations, including the alimentary tract, intravenous pyelography, and abdominal aortography among others, revealed nothing abnormal. Sometimes mild...
Table 1

<table>
<thead>
<tr>
<th></th>
<th>Neutrophils (number of lobes in per cent)</th>
<th>Eosinophils</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unsegm</td>
<td>2</td>
</tr>
<tr>
<td>A. P.</td>
<td>13</td>
<td>50</td>
</tr>
<tr>
<td>V. P.</td>
<td>66</td>
<td>31</td>
</tr>
<tr>
<td>A. S.</td>
<td>55</td>
<td>39</td>
</tr>
<tr>
<td>S. P.</td>
<td>45</td>
<td>48</td>
</tr>
<tr>
<td>T. H.</td>
<td>58</td>
<td>38</td>
</tr>
<tr>
<td>Pe. P.</td>
<td>19</td>
<td>47</td>
</tr>
<tr>
<td>T. P.</td>
<td>6</td>
<td>28</td>
</tr>
<tr>
<td>Pa. P.</td>
<td>4</td>
<td>30</td>
</tr>
<tr>
<td>V. S.</td>
<td>17</td>
<td>48</td>
</tr>
<tr>
<td>H. S.</td>
<td>5</td>
<td>37</td>
</tr>
</tbody>
</table>

Average normal according to Arneth
(Hämatorologische Tafeln, Sandoz AG, 2. Auflage, Basel 1972)

Typical heterozygous Pelger–Huet
(Hämatorologische Tafeln, id.)

|         | 54 | 45 | 1 | — | — |

The differential counts, at least 500 neutrophils and 50 eosinophils examined for each count. Blood specimens were taken during healthy intervals.

Sideropenic anemia was found: it improved by oral iron. There were no signs of hemolysis. Porphobilinogen, porphyrins, 5-HIAA, catecholamines, and enzyme tests for pancreatic and hepatic disorders were examined repeatedly during and between the attacks and found normal—as, for example, serum proteins and fibrinogen, immunoglobulins, the fourth component of complement and the inhibitor of the first, and the urinary excretion of etiocholanolone and other 17-ketosteroids. Neuropsychiatric examination gave no evidence for abdominal epilepsy or hysteria. The gynecologic status was normal.

During the attack ESR rises up to 50–70 mm/hr, being, at intervals, in the range of 20–40 mm/hr. The preexisting, strong left shift in the neutrophils becomes even more prominent, and there is a slight neutrocytosis with relative lymphopenia. The nuclei of the neutrophils are almost entirely unsegmented or bilobed (Table 1). The nuclear chromatin is coarse and lumpy. Most bilobed neutrophils have roundish lobes arranged in a "pince-nez" form, which is typical of the Pelger–Huet anomaly (Fig. 1). The segmentation of the eosinophils is also disturbed (Table 1).

Fig. 1. (Left) Typical bilobed neutrophil with clumped chromatin from Proposita. (Right) For comparison, normal bilobed neutrophil with more evenly staining chromatin and unequal lobes from the healthy sister T. P. Giemsa stain.
and some unusual stab basophils are found. The phagocytic activity and bacterial killing capacity of the neutrophils was tested and found normal. Alkaline phosphatase had a normal score. The karyotype was normal, determined from sternal marrow and peripheral blood.

Three sisters of proposita, a 35-yr-old nurse (A. S.), a 26-yr-old textile worker (S. P.), and a 23-yr-old secretary (T. H.), have also suffered from paroxysmal attacks of abdominal pain since childhood or adolescence. The attacks usually occur at intervals of 2-5 wk, but sometimes there have been remissions of several months. (A. S. has two children; during the pregnancies she was completely free from symptoms.) The attacks last 4-5 days, and a slight rise in temperature is constant. On several occasions, when recorded, ESR has been found to rise from 10-20 mm/hr to 40-50 mm/hr. A. S. was once laparotomized because of suspected appendicitis during a pain attack. Appendix was intact, but in the middle of the small intestine, for a length of 20 cm, the bowel was inflamed and edematous. There were plenty of enlarged lymph nodes, the histologic examination of which showed a nonspecific inflammation. Sometimes during the attacks A. S., S. P., and proposita have sterile craterlike ulcers in the buccal mucosa. Between the attacks, the sisters have been in good health. Extensive examinations in different hospitals have not clarified the etiology of the pain bouts. All the sisters have a segmentation arrest of granulocytes, which has been regarded as the benign Pelger-Huet anomaly. The segmentation of the neutrophils is almost completely stopped at the three-lobe level and eosinophils are also involved. The nuclear morphology is similar to that of proposita, resembling the Pelger-Huet anomaly.

The mother (A. P.) of the sisters, one brother (Pc. P.) and the son (V. S.) of A. S. have a partial segmentation arrest of neutrophils, eosinophils are normally segmented; the nuclear morphology is principally normal. They have not had abdominal pains or fever attacks. One sister (T. P.) and one brother (Pa. P.) and the daughter (H. S.) of A. S. have normal leukocytes and are healthy. The father is dead; he had no abdominal pains.

DISCUSSION

The family presents a puzzling association of a segmentation arrest of granulocytes with unexplained attacks of abdominal pain and fever.

The granulocyte anomaly of the four sick sisters resembles the Pelger-Huet anomaly, but the abundance of three-lobed neutrophils and the finding of one four-lobed cell from S. P. is atypical (Table 1). The partial segmentation arrest of the three other members of the family does not fit the classic Pelger-Huet anomaly. Weakened variants ("half typical cases") of this kind among the Pelger families have been reported earlier,1,2 but the variability of the degree of the segmentation arrest has not been so marked as here. The members of the families had no clinical complaints either. There is some room for speculation about the genetic background of the present anomaly, because the father and all his sibs are dead and nothing is known about their leukocytes. But on the basis of data obtained it seems clear that an unknown morbid gene with marked variability in expressivity is inherited from the mother. With full-blown expressivity the phenotype of the Pelger-Huet anomaly is simulated, and clinical symptoms appear.

The symptoms mimic familial Mediterranean fever (FMF), which belongs to the periodic disease syndromes, collectively entitled "periodic disease" by Reimann.3 In the history of FMF patients rheumatic heart disease, remission of symptoms during pregnancy, and unspecific laparotomy findings are typical features,4 found here too. In fact, the clinical picture of the present disorder with recurrent fits of pain and fever would warrant the designation "periodic disease." However, no abnormalities in leukocytes have been found in FMF or any other periodic disease, nor any etiology established. Whether the segmentation arrest of granulocytes and the symptoms are independent manifestations of
a common basic disorder or whether there is a direct causal connection between them remains to be questioned.

REFERENCES

1. Kokubo Y: One case of Pelger's familiar nuclear anomaly of leucocytes (the first case reported in Japan); Recommendation of two expressions: 'pseudo-myelocyte' (Undritz) and 'pseudo-metamyeloocyte' and suggestion of 'half typical Pelger's anomaly.' Tohoku J Exp Med 29:519, 1936.
Recurrent Attacks of Abdominal Pain and Fever With Familial Segmentation Arrest of Granulocytes

J. Murros and A. Konttinen