Oesophageal hiatus hernia in three generations of one family

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SUMMARY A family is described in which eight members in three successive generations had a sliding type of oesophageal hiatus hernia (or partial thoracic stomach) as a sole anomaly. The trait in this family behaved as a strict dominant, manifesting the segregation of a single abnormal autosomal gene. Other possible aetiologies are discussed but considered unlikely.

An oesophageal hiatus hernia has seldom been documented in more than one member of a family. In this paper we describe a family with eight unequivocally affected members in three successive generations; discuss possible mechanisms of inheritance; and review the literature on familial cases.

Investigation of the M. Family

The proposita, G.McC, aged 41 years (III.18 in the pedigree figure), was ascertained while in hospital for repair of an oesophageal hiatus hernia. Enquiry revealed that other members of her family had a similar lesion, and it was therefore decided to investigate the family fully. Accordingly, as many family members as possible were visited by both of us and detailed clinical histories taken. One of us (I.J.C.) examined by barium swallow and fluoroscopy all surviving descendants of II.9 (mother of the proposita) in generations IV and V and those surviving sibs of the proposita (III.18) who had not been previously examined, namely, III.22-24, a total of 27 subjects. No one interviewed refused radiological examination. Pertinent information on 'affected' and 'equivocally affected' members (see definitions below) is for convenience summarized in the Table; the essential pedigree with legends is given in the Figure.

CLASSIFICATION OF FAMILY MEMBERS
To arrange in categories members of the family with respect to their hiatus hernia (or partial thoracic stomach) status is complex and based on several criteria. To show a coherent pedigree, certain symbols and grouping under convenient descriptive terms for easy reference have been adopted. These terms and criteria are now explained.

'Affected' individuals
These individuals were found to have unequivocally positive radiological findings with or without the presence of characteristic symptoms. Only one such member (III.26) was in fact symptom-free at the time of radiological diagnosis.

'Equivocally affected' individuals
These individuals had strongly suggestive symptoms with negative or equivocal radiological findings. Individual III.21, who died aged 2½ years without having been radiologically examined, is also included in this class in view...
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<table>
<thead>
<tr>
<th>Family Reference</th>
<th>Date of Birth</th>
<th>Age at Onset of Symptoms (yr)</th>
<th>Symptoms</th>
<th>Radiological Findings (Age at Examination in Years)</th>
<th>Surgical Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Affected Members</td>
<td></td>
<td></td>
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<tr>
<td>C.M. II.9</td>
<td>12. 2.98</td>
<td>24, coinciding with first pregnancy</td>
<td>Heartburn and vomiting during last trimester of all pregnancies. Repeated haematemeses—first occasion December 1937. Retrosternal pain—worse at night. Waterbrash.</td>
<td>Hiatus hernia (54)</td>
<td>+</td>
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<tr>
<td>J.M. III.17</td>
<td>6. 8.22</td>
<td>12-15</td>
<td>Frequent vomiting when at school with difficulty in swallowing lumpy food. These symptoms, plus heartburn, waterbrash, and retrosternal pain persisted in variable degree up to time of diagnosis. Waterbrash, heartburn, retrosternal pain, and vomiting. Blood in vomit first occurred when 41 years. Vomiting with frequent haematemeses, heartburn, waterbrash, retrosternal pain radiating to left arm and occasional dysphagia with solid food.</td>
<td>Hiatus hernia (44)</td>
<td>+</td>
</tr>
<tr>
<td>G.McC. III.18</td>
<td>18. 5.24</td>
<td>29</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>A.M. III.20</td>
<td>20. 3.26</td>
<td>20-25</td>
<td></td>
<td></td>
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<tr>
<td>E.M. III.26†</td>
<td>31.12.37</td>
<td>25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>R.M. III.27</td>
<td>6. 5.41</td>
<td>5</td>
<td>Frequent severe vomiting attacks with haematemeses throughout childhood. Occasional dysphagia with solid food. Heartburn.</td>
<td>Hiatus hernia (23)</td>
<td>+</td>
</tr>
<tr>
<td>W.McC. IV.15</td>
<td>13.11.51</td>
<td>Birth</td>
<td>Persistent vomiting—often bloodstained. Operation for pyloric stenosis—diagnosis not confirmed. Intractable vomiting leading to death at 6 months.</td>
<td>Hiatus hernia (20)</td>
<td>+</td>
</tr>
<tr>
<td>Equivocally Affected Members</td>
<td></td>
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<tr>
<td>L.M. III.21</td>
<td>6.12.27</td>
<td>Birth</td>
<td>Persistent vomiting becoming particularly intractable during the 10 weeks preceding death at 24 years. Frequent haematemeses. Very underweight. At first vomited about once a week increasing to at least once a day at 6 years. Great reduction in frequency of symptoms when last seen at 6 yr 7 mth. No history of haematemeses. No dysphagia.</td>
<td>Partial thoracic stomach (5 months)</td>
<td>None</td>
</tr>
<tr>
<td>J.M. IV.9</td>
<td>7.11.60</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>J.McC. IV.16</td>
<td>21. 3.53</td>
<td>Infancy</td>
<td>Frequent vomiting of milk foods during infancy and difficulty encountered in weaning on to more solid diet. At 12 years symptom-free except for tendency to vomit on relatively slight provocation. Attended hospital at 141 years because of retrosternal pain after meals during previous 10 months. Relief obtained with antacids. Waterbrash + No dysphagia and no vomiting at this time.</td>
<td>1 Spontaneous gastro-oesophageal reflux on 2 occasions. No other abnormality defined: (6 yr 3 mth) 2 Negative (6 yr 7 mth) Negative (12 yr 5 mth) (14 yr 9 mth)</td>
<td>None</td>
</tr>
<tr>
<td>P.McC. IV.14</td>
<td>19. 6.50</td>
<td>?</td>
<td>Last heard of at 18 years. At that time was complaining of vomiting episodes for previous 6 months. No vomiting before that. No haematemeses. Frequent heartburn for years. Some relief obtained with antacids. Very slow over meals and has always required to have food finely minced or mashed.</td>
<td>Negative (12 yr 4 mth) (15 yr 2 mth) (18 yr 0 mth)</td>
<td>None</td>
</tr>
<tr>
<td>A.M. IV.21</td>
<td>26. 3.57</td>
<td>Infancy</td>
<td>Occasional vomiting during infancy. No haematemeses. Has always required to have food finely minced. Refuses or rejects all types of lumpy food, eg, meat, apple and tomato skin, bread crust, etc.</td>
<td>No reliable information</td>
<td>(8 yr 6 mth)</td>
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Table: Information on affected and equivocally affected members of the M. family

†The hiatus hernia in this patient was discovered on routine mass radiography two years before onset of any dyspeptic symptoms.

of the characteristic clinical history. (Negative radiological findings, even when recorded on more than one occasion, do not necessarily preclude the presence of a hiatus hernia and it is therefore possible that some of the young persons in this class may be shown to have the disorder on future radiological examination.)

'Affected' individuals

These individuals had no suggestive symptoms and negative radiological findings.

'Presumed affected' individuals

Persons with no suspicious symptoms (based on reliable history) and on whom no radiological examination was performed.

No reliable information

For some, exclusively earlier and collateral,
members of the pedigree no reliable data were available. Their status is therefore undetermined.

Discussion

The sliding type of oesophageal hiatus hernia in adults has, during the past 20 years, been the subject of numerous publications relating in toto to thousands of patients. A radiologically indistinguishable, but not necessarily identical, gastrooesophageal anomaly has also been described, though far less frequently, in infants and young children (Carré, Astley, and Smellie, 1952; Carré and Astley, 1960; Carré, 1959 and 1969). The anomaly in children, previously termed a 'congenital short oesophagus', is now usually called a 'hiatus hernia' though Carré has consistently preferred the term 'partial thoracic stomach' to avoid the implication of a known pathogenesis. The relationship between the adult and childhood lesion is unclear.

Though the condition in both adults and children is generally sporadic, examples of familial aggregation have been recorded; in only a very few families, however, have both adults and children been affected. Twenty sibships containing as the sole family cases more than one unequivocally affected member (other than monovular twins) have been described, viz, one each by Clerf and Manges (1934), Wamberg (1947, also in Thomsen, 1955), Thomsen (1955), Masse and Bader (1957), Bouma (1962), Sidd, Gilliam, and Bushueff (1966), Chaiken (1968) and 13 by Carré (1966); in a further 12 families, viz, one each described by Myles (1939), Sée (1947) and Roviralta (1952), two by Chaiken (1968), and seven by Carré (1957), the condition has been documented in two successive generations, although in the family reported by Sée one of the affected individuals had a paraoesophageal hiatus hernia; in another family (Chaiken, 1968) members of three consecutive generations were affected, though the two members of the F2 generation had paraoesophageal hiatus hernias; while in addition three of five published sets of monovular twins were concordant (Carré, 1957; Masse and Bader, 1957; and Sidd et al, 1966) and two discordant (Henry, 1954; Carré, 1957) for the trait. These data indicate a seeming role for heredity though the facts available are insufficient for its exact nature to be determined. Since, however, there is inter alia great disparity in the age of onset of symptoms in the cases quoted above and since other congenital anomalies not infrequently accompany the lesion in children to comprise sporadic (Thomsen, 1955; Carré, 1957) and familial (Masse and Bader, 1957) pleiotropic syndromes, a
heterogeneous aetiology is probable. Detailed consideration of these factors and segregation analysis, based on a personal series (I.J.C. of 356 children with a partial thoracic stomach, will be published separately.

In the M. family described here complex hypotheses need not be formulated since evidence to support simple autosomal dominant inheritance due to a single abnormal gene is strong. A hiatus hernia (or partial thoracic stomach) is the only demonstrable anomaly in affected subjects; transmission is documented through three successive generations; males and females are affected in equal proportions; affected and equivocally affected individuals are never born to parents who are both unaffected; and in the three sibships containing affected individuals, viz., those containing subjects II.9, III.18, and IV.15, approximately equal numbers of persons are affected or equivocally affected (11) and unaffected or presumed unaffected (9). Any differences in clinical expression could be ascribed to customary phenotypic variation and any presumption of an earlier age of onset in later generations could be attributed to the phenomenon of 'anticipation' (Penrose, 1948). The obvious alternative hypothesis of intermediate inheritance, that is, that the affected are homozygous, and the equivocally affected heterozygous for an abnormal gene, can be rejected with confidence since many individuals who are obligate heterozygotes ex hypothesi show no evidence of the trait even though of an age at which their affected relatives do so, and it is highly improbable that, without assortative mating, I.5, II.1, and III.19 (who originated from very different parts of Ireland) would be heterozygous for this presumably uncommon gene as they would necessarily be ex hypothesi.

It could, however, be argued that the affected members of the M. family represent more than one relevant genotype: particularly, that the proposita (III.18) and her affected sibs manifest a recessively inherited trait; their mother (II.9) and her only affected grandchild (IV.15) are sporadic cases of different aetiology, in the case of II.9 not improbable on population estimates of prevalence (Mobley and Christensen, 1956); and the equivocally affected individuals are in fact unaffected and owe their diagnostic status to a biased history given by affected parents alert to any suspicious symptoms in their offspring. This, and other hypotheses of aetiological heterogeneity, are statistically highly improbable in this pedigree, and in addition the fact that II.9 had symptoms from the age of 24, which is young for adult sporadic cases but not for affected parents of children with a partial thoracic stomach (Carré, unpublished data), is not supportive. Other, more general hypotheses, including that of an inherited diathesis to the condition, e.g., some structural defect of the diaphragmatic crura, requiring some additional factor or factors to produce the overt lesion, are impossible to test rigorously and are not discussed here.

This paper and the literature clearly indicate a genetic role in the aetiology of hiatus hernia (or partial thoracic stomach) in some families. This is important inter alia in genetic counselling, but unfortunately clinical and radiological criteria cannot at present differentiate aetiological types. It is probable that on balance the literature underestimates the true aggregation of cases in families: however, the contribution of inheritance to the phenotype will remain impossible to determine until many more detailed family studies have been conducted. Since the lesion may remain symptomatically silent, as demonstrated in individual III.26, such studies must include the radiological investigation of symptom-free as well as clinically affected individuals, as was undertaken in the M. family.

We wish to thank Mr J. A. W. Bingham for referring the proposita to us and Drs F. Shepherd, H. Simpson and W. T. Bailie, the family's general practitioners, for their help.

References


