Familial hiatal hernia in a large five generation family confirming true autosomal dominant inheritance

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Abstract

Background—Familial hiatal hernia has only rarely been documented.

Aims—To describe the pattern of inheritance of familial hiatal hernia within an affected family.

Subjects—Thirty eight members of a family pedigree across five generations.

Methods—All family members were interviewed and investigated by barium meal for evidence of a hiatal hernia.

Results—Twenty three of 38 family members had radiological evidence of a hiatal hernia. No individual with a hiatal hernia was born to unaffected parents. In one case direct male to male transmission was shown.

Conclusions—Familial inheritance of hiatal hernia does occur. Evidence of direct male to male transmission points to an autosomal dominant mode of inheritance. (Gut 1999;45:649-652)

Keywords: familial hiatal hernia; Barrett's oesophagus; autosomal dominant genetics

Hiatal hernia is a common disorder and most cases are isolated. Familial cases in more than one generation are rare and were first reported by Myles in 1939.¹ Other groups have similarly reported clusters of individuals with hiatal hernias across two or more generations of a

family.²⁻⁴ The mode of inheritance in these families has not definitively been established. As there is a preponderance of females, with no definite male to male transmission, the possibilities include either autosomal dominant inheritance with incomplete penetrance in males, X linked dominant inheritance, or mitochondrial inheritance.

Case histories

Twenty three definitely affected individuals are described within one family grouping (see fig 1 and table 1). The index case, V.4, a female, presented at the age of eight months with a history of vomiting dark brown blood and passing dark stools. The presence of a hiatal hernia with free gastro-oesophageal reflux was shown on a barium swallow. There was a history of hiatal hernia in her mother (IV.4) and her maternal grandmother (III.2). A full investigation of as many as possible of the family members was undertaken. Thirty eight members of a four generation pedigree were interviewed by IJC. All were examined radiologically with a barium swallow at which two observers were always present. An hiatal hernia was diagnosed by the presence of gastric mucosal folds above the diaphragm. Information was also obtained from at least two near relatives about five other family members (four deceased) who on the basis of their clinical history were in all probability similarly affected.

Figure 1 Five generation pedigree affected by infantile hiatal hernia. Individuals are shown as: affected (full shaded symbol), hiatal hernia on radiological examination; probably affected (hatched symbol), not radiologically examined; unaffected (clear symbol), negative radiological findings; no reliable information (diamond shape). Examined radiologically (+).

Table 1 Clinical summaries of “affected” and “probably affected” family members

Family reference	Age at onset of symptoms	Symptoms	Radiological findings (age)
<i>Affected members of family</i>			
II.2	Childhood	Frequent heartburn, worse at night. Waterbrash. Dysphagia with lumpy food. Repeated blood stained vomiting as a child.	HH (78 y)
II.8	Childhood	Troublesome heartburn—sleeps propped up. Much use of antacids. Waterbrash. Recent dysphagia with meat and fresh bread. Occasional vomiting.	HH (69 y)
III.1	10–15 y	Greatly troubled with heartburn and waterbrash.	HH (57 y)
III.2	Childhood	Recalls having heartburn and waterbrash when schoolchild. History of blood stained vomiting, heartburn, and chest pain radiating to left arm. Much improved following repair of HH at 50 y. Recurrence of swallowing difficulties, heartburn, and waterbrash 10 y later. Found to have an adenocarcinoma. Died when aged 64 y.	HH and stricture (61 y)
III.3	10 y	Frequent heartburn and waterbrash and occasional chest pain. Blood stained vomiting as a child.	HH (50 y)
III.6	Childhood	Heartburn and waterbrash. On cimetidine.	HH (53 y)
III.9	Childhood	Severe heartburn especially at night and after eating spicy food and chocolate. Waterbrash. Chest pain radiating to jaw and shoulder.	HH (50 y)
III.13	25 y	Frequent heartburn. Chest pain radiating to left arm. Some relief with antacids.	HH (36 y)
III.15	30 y	Frequent vomiting, heartburn, and waterbrash.	HH (35 y)
IV.3	18 y	Heartburn and occasional vomiting.	HH (20 y)
IV.4	25 y	Frequent heartburn, periodic vomiting and occasional dysphagia from first pregnancy. When 50 diagnosed as having a columnar lined lower oesophagus. On omeprazole and free of symptoms when last reviewed at 52.	HH (28 y)
IV.5	13 y	Recurrent episodes of heartburn and waterbrash with occasional dysphagia.	HH (26 y)
IV.7	10 y	Troublesome heartburn especially at night.	HH (21 y)
IV.11	18 y	Heartburn and waterbrash.	HH (22 y)
IV.14	Childhood	Heartburn with fatty foods and waterbrash.	HH (17 y)
IV.16	–	No symptoms.	HH (11 y)
IV.22	–	No symptoms.	HH (9 y)
V.3	12 y	Initially frequent heartburn with intermittent episodes of vomiting and dysphagia. Symptoms controlled with omeprazole. Surgical repair of HH aged 25.	Negative (2 y) Negative (10 y) HH (14 y) HH (16 y)
V.4	Birth	Blood stained vomiting from birth. Gradual reduction in vomiting frequency. Symptom-free from 2–9 y. Then suffered from a recurrence of vomiting and heartburn. Fundoplication when 10. Improved but required repeat fundoplication at 14 for return of symptoms. Barrett's oesophagus diagnosed at 23. On omeprazole and clinically well when last heard of at 24.	HH (8 m) HH (15 m) HH (4 y) HH (7 y) HH (10 y)
V.5	5 y	Heartburn and dysphagia. Fundoplication at 6 y. No further symptoms up to last review at 19.	HH (5 days) HH (2 y) HH (5 y)
V.6	–	No symptoms apart from very occasional heartburn when last reviewed at 12.	Negative (4 days) Negative (6 m) Negative (2 y) HH (3 y) HH (9 m)
V.7	Birth	Recurrent attacks of vomiting—much improved by 5 y. No complaints when last reviewed at 9 y.	HH (6 m) HH (2 y)
V.9	Birth	Vomiting, occasionally blood stained, for first 9 m. Then symptom-free to last review at 11 y.	
<i>Probably affected members</i>			
I.1	?	Suffered from her teens with severe heartburn for which she took large quantities of baking soda.	–
II.4	?	Had long history of vomiting and dyspepsia.	–
II.5	?	Suffered from much heartburn and attacks of vomiting from early childhood. Took baking soda regularly.	–
II.7	?	Heartburn and indigestion “all her life”. Always taking “medicines” for this.	–
IV.2	Childhood	Greatly troubled with heartburn when last heard of at 24 y.	–

HH, hiatal hernia.

Of the 38 members, 23 were shown to have an hiatal hernia; three of these were symptom free (IV.16, IV.22, V.6). Fifteen had negative radiological findings (were unaffected); all were without symptoms. Hiatal hernia with gastro-oesophageal reflux was the only demonstrable abnormality in affected individuals. Two individuals (mother and daughter) are known to have columnar lined (Barrett's) oesophagus (IV.4, V.4). A third member (grandmother, III.2) died from an oesophageal adenocarcinoma.

Of the 23 affected members, six were men and 17 women; four of five “probably affected” individuals were female. A more accurate assessment of sex distribution is provided by an analysis of fully investigated families (those in which all members were radiologically examined), namely 11.2 (omitting incompletely studied descendants of III.1), II.5, and II.7. In these families, six (46%) of 13 men and 14 (64%) of 22 women were affected. This difference was not statistically significant.

The pedigree shows transmission of the trait through four generations. All affected members had one affected or probably affected parent (no affected individual was born to unaffected parents). Direct male to male transmission is shown between father (IV.5) and son (V.9).

Discussion

A familial occurrence of hiatal hernia was first suggested 50 years ago.¹ Since then there have been several reports documenting hiatal hernia among siblings. Only a few have reported cases across generations. In 1968, Chaiken reported four families within two affected generations.⁵ In 1969, Goodman *et al* described a family in which six members (five women) across two generations were affected.³ In 1970, Carré and Froggatt described a family in which eight members were affected in three successive generations.² More recently, Leung has reported three families with clusters of gastro-oesophageal reflux and hiatal hernia in more than one generation.⁶ In addition, there is one series of 13 affected members across four generations⁷ and another report of both a mother and her son having been diagnosed as having an hiatal hernia at the age of two months.⁸

Interpreting these studies is difficult for several reasons. Firstly, the majority involve only adults and it is known that hiatal hernia is a common occurrence among adults, especially with increasing age.⁹ When studied by barium meal, this incidence was found to be 30–33% of adults. There was no difference in incidence between an asymptomatic population (33%)

and patients with gastrointestinal symptoms (30%).¹⁰ Investigating older generations of a young adult proband may simply show a chance association. This is less likely when infantile hiatal hernia is involved as its incidence has been estimated at 500 per 100 000 live births (0.5%) in the population.¹¹ When 271 younger siblings of children with hiatal hernia were examined, their chance of having an hiatal hernia was increased more than 20-fold to 12.5%.¹² Secondly, some studies combine cases showing gastro-oesophageal reflux but no hiatal hernia with definite hiatal hernia cases⁶ or include cases of paraoesophageal hernia.⁵ Thirdly, there is very limited examination of other family members. Since an hiatal hernia can be symptomatically silent,^{13 14} symptom free as well as clinically affected members should be investigated when undertaking detailed family studies.

To report accurately the familial link in hiatal hernia, it is important that the form of hiatal hernia is accurately defined, simple gastro-oesophageal reflux is excluded, cases as young as possible are investigated, and as many of the extended family as possible are examined. This study fulfils these criteria and represents the largest investigation into familial hiatal hernia to date.

In total, 23 definitely and five probably affected individuals were shown across five generations. Crucial to interpreting the genetics of the inheritance is the transmission from father (IV.5) to son (V.9), both of whom had symptoms from childhood or birth and both of whom had hiatal hernia proved radiologically. This effectively establishes the mode of inheritance as autosomal dominant and excludes X linked dominant inheritance or mitochondrial inheritance.

Carre and Froggatt suggested an autosomal dominant mode of inheritance² but were unable to show male to male transmission of definitely affected individuals. Similarly, in the other large family series, Sillero *et al* also suggested autosomal dominant inheritance, a 46 year old father and 14 year old son both having hiatal hernia.⁷ All other studies suggesting autosomal dominance as a mode of inheritance were of adults, increasing the possibility of chance association. Pure autosomal dominant inherited hiatal hernia however, is probably rare, and there is almost certainly genetic heterogeneity in hiatal hernia. The situation may be similar to hereditary and "sporadic" breast and bowel cancers where 5–10% of these common cancers have an autosomal dominant pedigree, and the remainder are due to either non-heritable factors or low penetrance cancer genes. We cannot state that the pedigree shows unequivocal autosomal dominant inheritance. Although the spouses of cases have no evidence of hiatus hernia on clinical history, there is a small possibility of them being asymptomatic gene carriers, in which case recessive or polygenic inheritance could be a possibility. At present, although this family would be suitable for genome wide scanning to allow linkage or mapping of suitable hiatal hernia genes, DNA is not yet available from

enough family members to allow this. Such approaches would allow elucidation of the genetics of hiatal hernia and will help to explain why such highly penetrant families are rare, and whether similar genes are involved in the pathogenesis of more common polygenic hiatal hernia.

Previous studies have noticed a female predominance and suggested incomplete penetrance in men.^{3 5} Despite the overall appearance of female predominance in our study (75%), the figures for the most extensively investigated family stems were six (46%) men and 14 (64%) women being affected. These figures were not statistically significantly different and do not require the added hypothesis of incomplete male penetrance.

However, independent of gender, the clinical expression was very variable. Of the 23 definitely affected cases, three first developed symptoms at birth, 12 in childhood, five as adults, and three remain asymptomatic. That three of the most recent generations (V.4, V.7, and V.9) developed symptoms at birth could raise the possibility of anticipation.¹⁵ This pedigree however, is too small on which to base an accurate judgement, and analysis of further pedigrees will be needed to clarify this. Clinical ascertainment bias (finding affected individuals earlier because of earlier looking for them) may not fully explain these cases as they all presented clinically with severe symptoms.

Long term follow up studies^{13 14} have shown that an infantile hiatal hernia will persist into adult life in about half the patients. However, its persistence was not associated with increased symptoms as adults or increased antacid use compared with those with no demonstrable hiatal hernia. Even if all infantile hiatal hernia were to persist or recur and give rise to symptoms in adult life, they would account for only a very small percentage of adult hiatal hernia—certainly less than 5%.

Of greater significance than the hiatal hernia itself is the possibility that it predisposes to ongoing reflux and development of Barrett's oesophagus. This family pedigree documents two cases of Barrett's oesophagus and one of oesophageal adenocarcinoma. Another recent publication also documented Barrett's oesophagus in a group of non-familial infantile hiatal hernia followed over 20–40 years.¹⁴

In conclusion, we have described a family in which 23 of 38 members had an hiatal hernia. In this family, autosomal dominant inheritance is confirmed by evidence of one male to male transmission.

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