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*Case report*

# Family occurrence of achalasia and diffuse spasm of the oesophagus

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SUMMARY **In view of the unknown aetiology of achalasia and diffuse oesophageal spasm we report four families (father/son, mother/son, brother/brother, cousin/cousin) with achalasia and oesophageal spasm examined by radiology, endoscopy and manometry. Family occurrence of oesophageal motor disorders supports the hypothesis that a genetic trait may play a role in the pathogenesis. The family coincidence of achalasia and oesophageal spasm supports a close relationship between the two diseases.**

Achalasia and diffuse oesophageal spasm of the oesophagus are diseases of unknown aetiology. Achalasia is characterised by the absence of peristalsis in the body of the oesophagus and a failure of the lower oesophageal sphincter (LOS) to relax in response to deglutition.[1] Simultaneous and repetitive contractions of high amplitude and long duration with a normal function of the LOS are the characteristics of diffuse oesophageal spasm. The yearly incidence of achalasia is 0·6 to 1·0/100 000.[2-4] Instances of reported family occurrence of achalasia have led to the hypothesis that genetic factors may be important in the pathogenesis of the disease. We report four families in which several members had symptoms of achalasia and diffuse oesophageal spasm, respectively (Table 1). Horizontal and vertical transmission occurred in these families, suggesting that endogenous as well as exogenous factors contribute to the disease.

## Family I

CASE 1

A 36 year old man with retrosternal discomfort for eight years and progressive dysphagia and intermittent regurgitation for one year before admission. Barium swallow showed moderate dilatation of the oesophagus, tertiary contractions, and absence of LOS relaxation. Oesophageal manometry revealed simultaneous contractions of low amplitudes and incomplete relaxation of the LOS in response to deglutition (Fig. 1, top). The patient became asymptomatic after pneumatic dilatation of the LOS.

CASE 2

A 64 year old father complained of moderate dysphagia, intermittent substernal pain in response to swallowing, occasional regurgitation, and symptoms worsening during stress over 14 years. Radiology revealed a markedly dilated and tortuous oesophagus with narrowing at the oesophagogastric junction (Fig. 2, left). At oesophagoscopy retention oesophagitis was found. Manometry showed hypomotility of the oesophagus and a failure of the LOS to relax. The patient refused therapy.

## Family II

CASE 3

A 50 year old man noticed dysphagia and regurgitation since puberty. The patient could take liquids only in an upright position. Cardiomyotomy and fundoplication were carried out at age 37 years. Two years later an epiphrenic diverticula was resected.

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After initial symptom improvement dysphagia reappeared seven years later. Radiology revealed spastic contractions in the middle and lower part of the oesophagus (Fig. 2, right). Hypermotility and pseudodiverticula were seen at oesophagoscopy. Oesophageal motility recordings, showed simultaneous high amplitude contractions (up to 500 mmHg) of prolonged duration (up to 13 sec) (Fig. 1, bottom). The patient was successfully treated with nifedipine for oesophageal spasms.

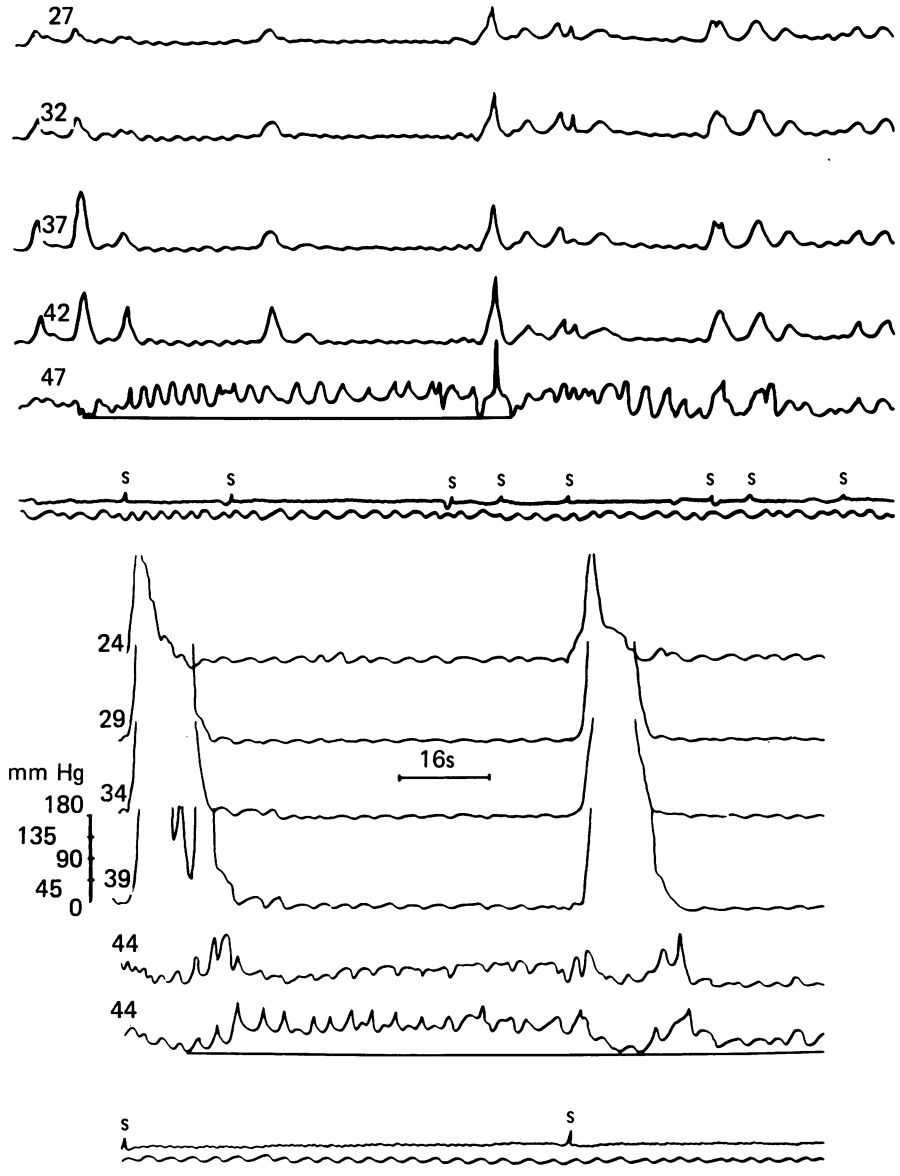


Fig. 1 (top): *Manometric registration in achalasia (son, family I). Registrations 47, 42, 37, 32, and 27 cm inc showing simultaneous contractions with low amplitude and absent LOS relaxation (47 cm inc) to fundic pressure in response to deglutition (s=swallows; bottom line: respiration recoding).* (bottom): *Manometric registrations in diffuse oesophageal spasm (son, family II). Registrations 44, 39, 34, 29, and 24 cm inc showing simultaneous contractions with high amplitude and prolonged duration and sufficient LOS relaxation (44 cm inc) to fundic pressure in response to deglutition (s=swallows; bottom line: respiration recording).*

Table 1 *Clinical features and diagnostic findings in eight patients with family dysphagia*

| *Patient* | *Symptoms* | *Radiography* | *Endoscopy* | *Manometry* | |
|---|---|---|---|---|---|
| | | | | *Absent/ incomplete LOS-relaxation* | *Simultaneous contractions amplitude de-/increased* |
| 1 | Dysphagia<br>Regurgitation | Dilatation<br>Tertiary Contractions<br>Narrowing of oesophagogastric junction (OGJ) | Smooth<br>Narrowing of OGJ | + | + |
| 2 | Dysphagia<br>Regurgitation<br>Retrosternal pain | Dilatation<br>Narrowing of OGJ | Oesophagitis<br>Smooth<br>Narrowing of OGJ | + | + |
| 3 | Dysphagia<br>Regurgitation | Spastic contractions | Smooth<br>Narrowing of OGJ<br>Hypermotility<br>Pseudodiverticula | | + |
| 4 | Dysphagia<br>Regurgitation | Dilatation<br>Narrowing of OGJ | | | |
| 5 | Dysphagia | Dilatation<br>Diverticula<br>Narrowing of OGJ | Smooth<br>Narrowing of OGJ | + | + |
| 6 | Dysphagia<br>Substernal discomfort | Narrowing of OGJ<br>Tertiary contractions | Smooth<br>Narrowing of OGJ | + | + |
| 7 | Dysphagia<br>Retention of food | Dilatation<br>Narrowing of OGJ | Smooth<br>Narrowing of OGJ | | |
| 8 | Dysphagia | Dilatation<br>Narrowing of OGJ | Smooth<br>Narrowing of OGJ | + | + |

CASE 4

A 77 year old mother had experienced dysphagia and nocturnal regurgitation for 30 years. Radiology revealed a dilated oesophagus with narrowing of the oesophagogastric junction. The patient was admitted because of haematemesis. Development of an aspiration pneumonia and septicaemia caused by *E coli* impeded further diagnosis and therapy for the oesophageal disorder. The patient died from respiratory insufficiency. Postmortem examination, revealed a narrowed gastro-oesophageal junction (circumference 2·5 cm) and a dilated part of the mid and lower oesophagus (circumference of 7 to 10 cm) (Fig. 3).

At microscopy the circular muscle of the distal oesophagus was markedly hypertrophied and scarred, with numerous elastic fibres in between. The myenteric plexus was missed in the scarred part of the wall. Only a few ganglia showed degeneration. Mild inflammation was seen in the myenteric plexus. The neurone specific marker S-100 protein was found only in spots in the patchy scarred areas of the plexus, whereas the other parts exhibited diffused staining. The innervation in the hypertrophied muscle was thinned and neuropathologic examination of the vagus nerve and its nuclei, revealed no regressive transformation.

Family history, revealed severe dysphagia in the mother and sisters of this patient. One brother underwent surgery because of oesophageal stenosis (Fig. 4). No further data were available, however, because all the family had died.

**Family III**

CASE 5

A 71 year old man complained of dysphagia over a two year period with symptoms worsening with stress. Radiology revealed oesophageal dilatation and diverticula in the middle part. No organic stenosis or inflammation was found during endoscopy and oesophageal manometry showed only simultaneous pressure waves of low amplitude and a failure of the LOS to relax. Dysphagia improved after pneumatic dilatation.

CASE 6

The 74 year old brother suffered from postprandial retrosternal discomfort for 26 years and from

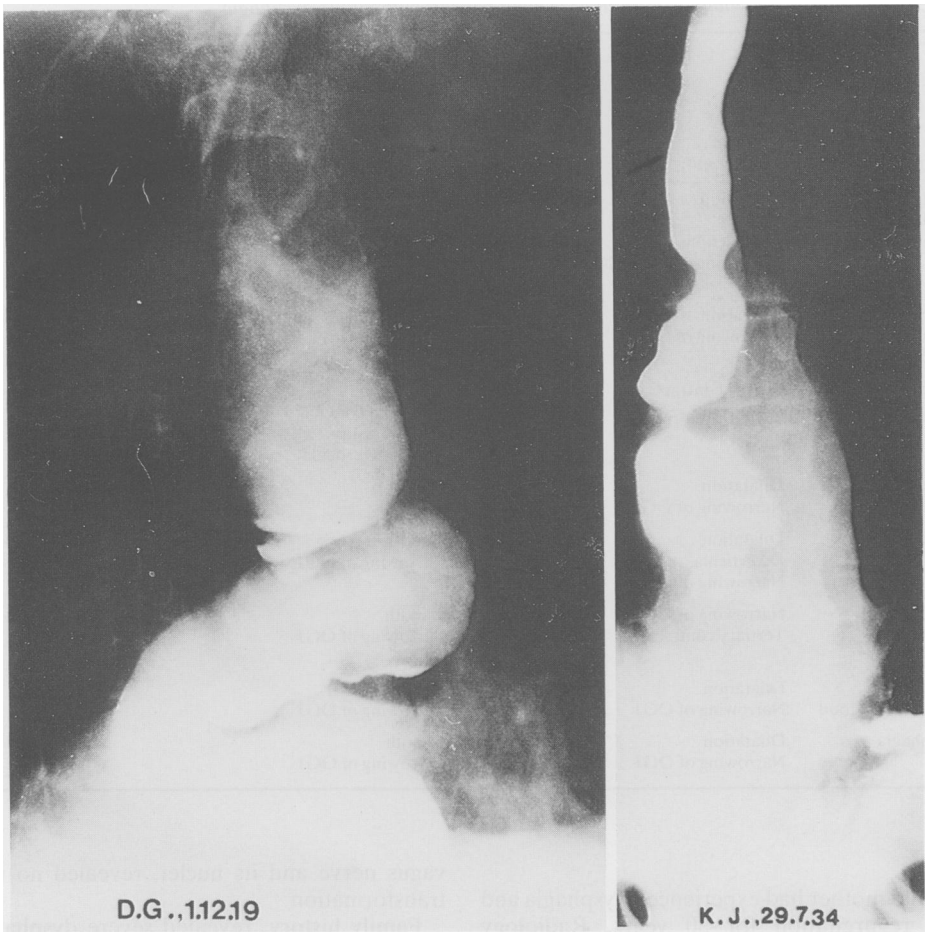


Fig. 2 (left): *Barium swallow of the oesophagus (father, family I) indicating marked sigmoideous dilatation.* (right): *Barium swallow (son, family II) in diffuse oesophageal spasm reveals segmentary contractions.*

progressive dysphagia over three years, before admission. Radiology showed oesophageal dilatation with tertiary contractions. Oesophageal manometry revealed simultaneous contractions and incomplete LOS relaxation. Intermittent peristaltic and repetitive pressure waves of high amplitude and prolonged duration led to the diagnosis of an atypical achalasia. Pneumatic dilatation of the LOS improved the symptoms, and substernal pain ceased with nifedipine.

**Family IV**

CASE 7

A 71 year old woman complained of progressive dysphagia and intraoesophageal food retention, for eight years with deterioration over the past 10 months.

A markedly dilated oesophagus with narrowing of the oesophagogastric junction was seen on *x*-ray examination. No organic lesions were found during endoscopy. Pneumatic dilatations brought no permanent symptom improvement. After cardiotomy and hemifundoplication a complete relief of symptoms was noticed. Postsurgical histological examination of a longitudinal muscle strip, showed neither scars nor malignancy.

CASE 8

A 76 year old female cousin suffered with severe dysphagia over 11 years, particularly during stress. A mega-oesophagus was seen radiologically. Endo-

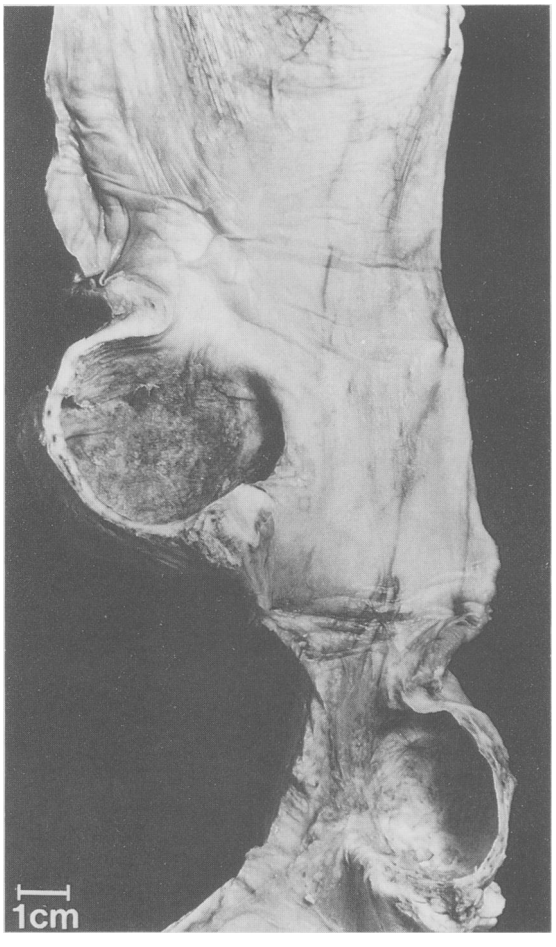


Fig. 3 *Postmortem examination (mother, family II) showing marked dilatation and diverticulous pouching of the oesophagus.*

scopy revealed a markedly dilated oesophagus with a narrowed oesophagogastric junction. Manometry showed raised oesophageal resting pressure, simultaneous contractions of low amplitude and a failure of the LOS to relax after deglutition. Repeated pneumatic dilatations improved the symptoms.

## Discussion

Family occurrences of achalasia are rare. The present observation, however, indicates that a carefully collected family history of oesophageal symptoms in family members of patients with achalasia, may help to detect and treat these cases early and thus prevent complications.

Family occurrences of achalasia suggest that genetic factors may play a role in the pathogenesis of this disorder. The mode of genetic inheritance of the disease, however, remains speculative at present, particularly because of the low occurrence rate of achalasia during childhood which suggests that other factors may play a major role in the manifestation of this illness. According to Swenson,[29] Payne,[30] and Moersch,[31] childhood accounts for less than 5% of all cases of achalasia. Likewise, the onset of symptoms in all patients of our study occurred after childhood. Thus, a multifactorial causation of oesophageal motor disorder becomes likely. It is suggested that there is a disposition to the clinical manifestation of achalasia, as soon as additional endogenous and exogenous factors, gain access.

From the literature it appears that there is a preponderance of horizontal transmission of oesophageal motor disorders (Table 2). To our knowledge only four families with a vertical transmission have been reported so far (Table 3). On the other hand, two of the four family cases presented document vertical transmission of the disease. Thus, the question arises whether this difference is caused by a selection bias in the clinical samples, or whether preponderance of horizontal transmission represents a systematic influence of endogenous or exogenous factors.

Assessment of vertical transmission, however, may be biased because of late symptom onset in

Table 2 *Family occurrence of achalasia with horizontal transmission*

| *References* | *Affected family members* | *Sex M/F* | *Age at onset (yr/mon)* |
|---|---|---|---|
| Ellis *et al*[4] | brother/brother/sister | M/F/F | 51/?/? |
| Allgrove *et al*[5] | brother/brother | M/M | 8·6/6·6 |
| | sister/brother | F/M | 6/9·8 |
| Badrawy *et al*[6] | brother/sister | M/F | <6 mon/2 mon |
| | brother/sister | M/F | <10 mon/? |
| Bosher *et al*[7] | brother/brother | M/M | 3 mon/3 mon |
| Cloud *et al*[8] | 4 family members | ? | childhood |
| Dayalan *et al*[9] | sister/sister/brother | F/F/M | 18 mon/11/ 12 mon |
| Di Bello*et al*[10] | brother/brother/brother | M/M/M | 20/20/? |
| Kay *et al*[11] | brother/sister | M/F | 34/32 |
| Koivukangas *et al*[12] | twins | F/F | 10/10 |
| Koteles *et al*[13] | brother/brother/brother | M/M/M | 5/4/6 |
| London *et al*[14] | brother/brother/brother | M/M/M | 34/56/64 |
| Nagler *et al*[15] | twins | M/F | 31/32 |
| Polonski *et al*[16] | sister/sister | F/F | 5/1 |
| Stein *et al*[17] | monozygotic twins | F/F | 39/25 |
| Stoddard *et al*[18] | brother/brother | M/M | 13/22 |
| Rozyki *et al*[19] | brother/sister | M/F | 20/19 |
| Thibert *et al*[20] | brother/brother (fam I) | M/M | 2/childhood |
| | brother/brother (fam II) | M/M | 1/5 |
| Tyce *et al*[21] | brother/brother | M/M | 29/24 |
| Uzunow *et al*[22] | sister/sister | F/F | 8 mon/birth |
| Vaughan *et al*[23] | brother/brother | M/M | 3/17 mon |
| Westley *et al*[24] | brother/brother/brother | M/M/M | 1/9 mon/3 |
| | brother | M | 18 mon |

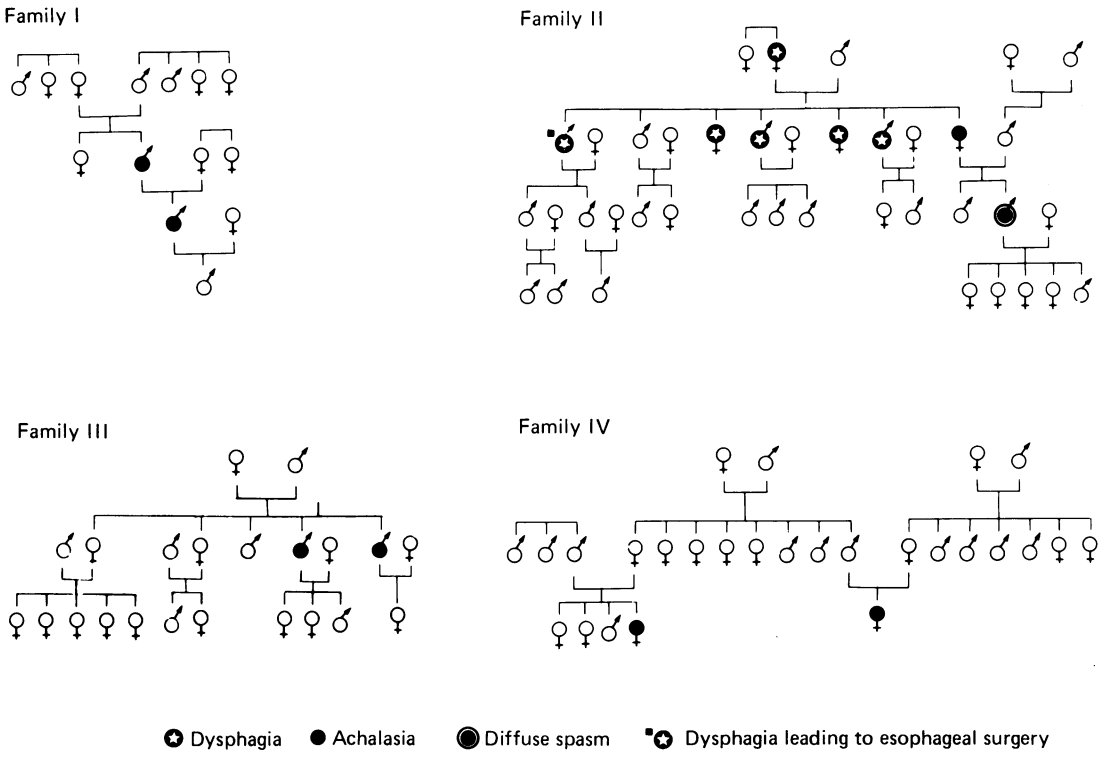


Fig. 4 *Pedigree of family I–IV: Horizontal transmission of achalasia in family III (left: case 5; right: case 6) and family IV (left: case 7; right: case 8). A vertical transmission of achalasia occurred in family I, a vertical transmission of achalasia and diffuse spasm in family II.*

oesophageal motor disorders, the likelihood that patients with clinical symptoms of achalasia being available for evaluation, may be decreased. Thus, vertical transmission may well exist, but its documentation may be difficult.

A preponderance of a horizontal transmission in achalasia, on the other hand, suggests inheritance through an autosomal recessive gene. In cases of animal achalasia as in the inbred wire fox terrier, the achalasia like symptoms were inherited through one locus of two allele with an autosomal recessive gene with penetrance in the homozygous state.[32] Horizontal transmission specifically suggests exogenous factors to be of importance, however, when no vertical transmission can be documented, even by verbal history.

In achalasia a degeneration and diminuation of the number of ganglia in the Auerbach's plexus and ultrastructural lesions in the vagus nerve and its nuclea have been described and discussed as potentially pathogenic factors.[33] In addition, disturbances in the sympathetic innervation and a reduced number of sphincter relaxating β-adrenoceptors, have been thought to contribute to the pathogenesis of the disease.[34] Neurotoxic infections similar to Chagas' disease are discussed.[35,36] Furthermore, a reduction of VIP-fluorescent nerves[37] and a coincidence of achalasia with different types of malignancy and sarcoidosis have been observed.[1,35,36,38–43] The cause, however, of the nervous lesion in unknown. In the present study the postmortem examination of the 77 year old lady would be in agreement with these investigators, where a reduction of ganglia in the distal part of the oesophagus was found.[44,45] A decrease of ganglia cells occurred particularly in the scarred diverticulum of the oesophagus.

Achalasia was detected in family I and IV and a hypercontractile pattern of achalasia in family III.

Table 3 *Family occurrence of achalasia with vertical transmission*

| *References* | *Affected family members* | *Sex M/F* | *Age at onset (yr)* |
|---|---|---|---|
| Chawla *et al*[25] | mother/son | F/M | 72/45 |
| Kilpatrick *et al*[26] | mother/daughter | F/F | 59/46 |
| Mackler *et al*[27] | son/father | M/M | 37/63 |
| Zimmermann *et al*[28] | son/father | M/M | 36/72 |

Diffuse oesophageal spasm occurred in the son of family II. Although achalasia and oesophageal spasm usually can be distinguished manometrically, both disorders are thought to be different expressions for a common underlying disorder. Transition from diffuse oesophageal spasm to achalasia and the occurrence of clinical and manometrical signs of both diseases have been reported.[46 47] Additionally, hypersensitivity of the LOS to cholinergic transmitters, is a common feature in achalasia and in diffuse spasm. The familial cumulation of both motility disorders supports the hypothesis of a close relationship.[48]

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