CASE REPORT

Familial history aggregation on acute appendicitis

Francesc Simó Alari,¹ Israel Gutierrez,¹ Judit Giménez Pérez²¹General surgery, Centre hospitalier du val d'Ariège, Foix, France²General practitioner, Hospital Universitari MutuaTerrassa, Terrassa, Barcelona, Spain**Correspondence to**
Dr Francesc Simó Alari,
f.simo.alari@gmail.com

Accepted 5 October 2017

SUMMARY

Appendectomy is the most commonly performed surgical procedure, affecting 1%–8% of the paediatric population, with a total 7% lifetime risk, most likely in adolescents and young adults.

A case of familial aggregation was reported in our hospital in a family composed of nine siblings from which six of them (66.6%) had been treated of acute appendicitis, five of them in our centre. Many factors have been described as predisposing to appendicitis. Several studies have highlighted the influence of genes in the evolution of this disease and its severity, demonstrating a relative risk increase by three when family history is present.

Family history of acute appendicitis is an important factor to be taken into consideration during the medical interview. Clinicians attempting to fine-tune their diagnostic accuracy when patients present with acute abdominal pain should inquire about family history of appendicitis.

BACKGROUND

Although acute appendicitis is frequent, it is subject to common misconceptions. Sometimes the diagnosis can be particularly difficult, especially in infants, pregnant women and in elderly patients. Many physicians are not aware there is a genetic predisposition in acute appendicitis described long time ago. Because the classic sequence of symptoms occurs in less than 66% of patients, doubts are made more evident. In the actual current technology-based medicine that tends to quit semiology, we think this article is important as it tries to draw the attention of other medical colleagues to the importance of a detailed medical history and a complete physical examination in order not to miss the diagnosis or to underestimate their severity.

With a simple, focused and accurate clinical history, many unnecessary procedures could be avoided.

CASE PRESENTATION

A case of familial aggregation was reported in our hospital in a family composed of nine siblings from which six of them (66.6%) had had acute appendicitis, five of them being treated in our centre (figure 1). First case was on a 27-year-old woman 1 month after giving birth, the other 5 cases in a age range from 16 to 19 years. The most common form of presentation was as phlegmonous appendicitis in five of them and purulent appendicitis in one, none of them showed perforated vermiform appendix during surgery. Laparoscopic

appendectomy was performed in all cases having no complications reported, with a median hospital stay of 1.4 days. While a single case was present in the paternal family branch composed of 11 siblings, 8 cases were reported in the maternal branch, composed of 16 siblings.

DIFFERENTIAL DIAGNOSIS

Epiploic appendagitis, pelvic inflammatory disease (PID) or tubo-ovarian abscess, mesenteric lymphadenitis, Mittelschmerz, ovarian cyst or torsion, ureterolithiasis and renal colic, Crohn's disease, acute pancreatitis, perforated duodenal ulcer and so on.

TREATMENT

All patients were treated by laparoscopic approach, nowadays gold standard for acute appendicitis.¹

OUTCOME AND FOLLOW-UP

All patients underwent a laparoscopic appendectomy, no incidences or complications were reported during their hospitalisation with an average stay of 1.4 days. A single-day follow-up in the outpatient area 10 days after surgery confirmed a correct evolution in all cases.

DISCUSSION

According to all emergency surgical procedures, appendectomy is actually the most commonly performed, with a total 7% lifetime risk.^{2–3} It appears most likely in teenagers and young adults, affecting 1%–8% of the paediatric population.^{4–5} It has been the subject of uncountable investigations since it was first described in 1884 by Fitz.⁶ Surprisingly however, despite being so common, its aetiology remains unknown and the role of inheritance has received little attention.

Although the exact mechanisms leading to this condition remain obscure, there is a widespread belief that luminal obstruction by external (lymphoid hyperplasia) or internal (faecal material, appendicoliths) compression plays a key pathogenic role. Nevertheless, several factors have been described as to predispose or influence on acute appendicitis development. The presence of an appendicolith on CT scan has been associated with a higher risk of antibiotic failure and recurrence when trying a non-surgical approach.⁷ The low-fibre intake theory, developed by Adamidis *et al*,⁸ faecolith formation^{9–10} or geographical distribution.^{11–12} Pregnant women, especially those on the third trimester, seem to have a lower risk.¹³ The classic aetiopathogenic theory has been the obstruction of the appendicular lumen^{14–15} by faecal material, lymphoid

CrossMark

To cite: Simó Alari F, Gutierrez I, Giménez Pérez J. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2016-218838

Figure 1 Family distribution of acute appendicitis. Male (■), female (●), gender not specified (◆). The number of patients is inside the figure, the ages at diagnosis on the bottom.

follicular wall thickening or foreign body. Besides being the most widely accepted theory, obstruction has been demonstrated in only 30%–40%,¹⁶ the mucous ulceration being the triggering element in all of them. This classic theory is actually being discussed in recent reviews.¹¹⁷

Symptoms of appendicitis overlap with a number of other conditions making sometimes diagnosis a challenge. Alvarado score,¹⁸ one of the most used so far, can be used to stratify patients with appendicitis-like symptoms; it enables risk stratification in patients presenting with abdominal pain, linking with a probability of appendicitis. It is a useful diagnostic tool based on clinical history, physical examination and laboratory parameters over a 10-point score.¹⁹ The key points for a prompt and correct resolution are a quick diagnosis, followed by an immediate surgical resection before it reaches an advanced inflammatory state. An accurate and correctly orientated anamnesis including family episodes could help to minimise the indiscriminate use of imaging diagnostic procedures.

On the other hand, several studies have demonstrated the influence of genes in this disease and its severity (table 1).

Downs suggested the possibility of an inborn malformation, after distinguishing a fibrous band in the appendicular base that could provoke its bending and kinking, causing lumen obstruction in 16 cases in 22 family members.²⁰ Besides such anatomical malformation by itself would not start the inflammatory process, it could be considered a predisposing factor to obstruct the appendicular lumen. Other authors have suggested that the position and orientation can be inherited as a dominant character. Baker was the first one to describe in 1937 the family

aggregation in a family with 50% of its members affected.²¹ Andersson *et al* and Arnbjörnsson described a high incidence of appendicitis in first-grade family members.^{22 23} Few cases have been published on simultaneous event in monozygotic twins.^{24 25}

Oldmeadow *et al*, through the Australian Twin Registry, described tobacco as a cofactor for appendicitis nor ligated to its intensity or duration; also, its cessation decreased the risk by 15% per year after quitting.²⁶ Sadr Azodi through the Swedish Twin Register (3441 monozygotic and 2429 dizygotic twins) found a total of 30% heritability in the appendicitis risk, being more intense in the female group.²⁷

Nyboe Andersen *et al*²⁸ have recently shown an association between acute appendicitis and ulcerative colitis (UC) through the National Denmark Register with 7.1 million individuals, showing a reduced risk of UC if individuals had had acute appendicitis before the age of 20 or a first-degree relative who had, especially in families with UC predisposition. However, appendectomy is not recommended to improve the disease course in patients with UC or to prevent its development in family members.

Gauderer *et al* in a prospective case-control paediatric population study conclude that ‘patients with appendicitis were twice as likely to have a positive family history as those with right lower quadrant pain (but no appendicitis), and almost three times as likely to have a positive family history as are surgical controls (without abdominal pain)’.²⁹ Drescher *et al* concluded similarly in adult population.³⁰ When concerning inborn immunity and response to local inflammatory process, Rivera-Chavez *et al* demonstrated an association between a polymorphism on a single nucleotide in the interleukin 6 (IL-6) gene (locus IL-6 – 174 allele C) and a lower risk of uncomplicated appendicitis.³¹

The most relevant study in this field was performed by Basta *et al* who wrote the first formal genetic analysis on this frequent disease. By studying the families of 80 patients, he found no evidence of a major gene involved, but a multifactorial or polygenic model with a 56% total heritability and a relative risk of 10.0 (95% CI 4.7 to 21.4), that varied in relation to kinship grade (21% for first-grade family, 12% for second-grade family and 7% for third-grade family).³² Basta *et al* showed that an association between phenotype CcD-Ee Rh³³ and the blood group A, when compared with the O group,³⁴ being found in more proportion in patients with appendicitis when compared with the control group.

Although being common, the diagnosis of acute appendicitis sometimes can be particularly difficult, especially in infants, pregnant women and in the elderly. Because the classic sequence of symptoms occurs in less than 66% of patients, various kinds of difficulties can be encountered when attempting its diagnosis.

Table 1 Studies demonstrating a genetic influence or familial aggregation in acute appendicitis

	Year	Type of study	n	Studied generations	Results
Andersson <i>et al</i>	1979	Prospective C&C	58	Third-degree generation	Suggest family predisposition
Arnbjörnsson	1982	C&C	73	Third-degree generation	Suggest family predisposition
Brender	1985	C&C	135	First-degree generation	Significant positive trend
Basta <i>et al</i>	1990	C&C	180	Paediatric <16 years third-degree generation	RR 10 (CI 4.7 to 21.4) Polygenic inheritance 56% heritability
Gauderer <i>et al</i>	2001	Prospective C&C	59	Paediatric <19 years First-degree generation	OR 2.0–2.9
Rivera-Chavez <i>et al</i>	2004	Observational	134	–	IL-6 polymorphism and appendicitis severity
Drescher <i>et al</i>	2012	Prospective C&C	116	Third-degree generation	OR 1.74–1.88

C&C, case-control; IL-6, interleukin 6; RR, relative risk.

Assuming a total heritability of 56%, relative risk increases by three when family history is present. Knowing that appendicitis has a non-negligible genetic background is remarkably important towards understanding its aetiology, orientate its diagnosis and enable an early surgery. Family history of acute appendicitis is an important factor to be taken into consideration when the anamnesis and medical interview takes place in a patient with pain in the right lower quadrant of the abdomen. Due to its potential value to adjust the indication threshold for other invasive procedures, a detailed family history should be obtained in any patient in whom an acute appendicitis is suspected or present in the differential diagnosis. In case diagnostic doubts remain, the advantages of ultrasonography as a first-line investigation for children (no radiation risk, relatively low price and 24 hours accessibility) make it the method of choice to confirm the diagnosis in paediatric patient when performed by an experienced radiologist. In adolescents and adults, CT scan has widely been accepted as the imaging strategy in most centres.³⁵

Further studies are still needed to be conducted to demonstrate a stronger association between genetic predisposition and acute appendicitis. Meanwhile, a complete medical and familial history remains an easy, quick and costless item to be taken into consideration. A history of first-degree relatives may be relevant during the emergency history taking. A prompt diagnosis followed by early treatment is recommended to reduce morbidity and mortality in risk groups. For now, clinicians attempting to refine their diagnostic accuracy when patients present with acute abdominal pain might inquire about family history of appendicitis.

Patient's perspective

- The patients' parents referred after knowing the results of our bibliographical review (translated to English): "Knowing there could be a familial predisposition to appendicitis, special care and advice will be placed in the rest of our family members when belly pain appears, rather than wait it to evolve".

Learning points

- The aetiopathogeny of appendicitis is multifactorial, including genetic factors (56%).
- Family history of acute appendicitis is an important factor to be taken into consideration, especially when echo/CT scan is not available.
- Patients with appendicitis are three times likely to have a positive family history.

Contributors FSA: dealt directly with case, writing the report, design and data collection. IG and JGP: dealt directly with case.

Competing interests None declared.

Patient consent Parental/guardian consent obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Bhangu A, Søreide K, Di Saverio S, *et al.* Acute appendicitis: modern understanding of pathogenesis, diagnosis, and management. *Lancet* 2015;386:1278–87.
- 2 Ergul E. Heredity and familial tendency of acute appendicitis. *Scand J Surg* 2007;96:290–2.
- 3 Stewart B, Khanduri P, McCord C, *et al.* Global disease burden of conditions requiring emergency surgery. *Br J Surg* 2014;101:e9–e22.
- 4 Scholer SJ, Pituch K, Orr DP, *et al.* Clinical outcomes of children with acute abdominal pain. *Pediatrics* 1996;98(4 Pt 1):680–5.
- 5 Reynolds SL, Jaffe DM. Diagnosing abdominal pain in a pediatric emergency department. *Pediatr Emerg Care* 1992;8:126–8.
- 6 Fitz RH. Perforating inflammation of the vermiform appendix. *Trans Assoc Am Phys* 1886;1:107–15.
- 7 Shindoh J, Niwa H, Kawai K, *et al.* Predictive factors for negative outcomes in initial non-operative management of suspected appendicitis. *J Gastrointest Surg* 2010;14:309–14.
- 8 Adamidis D, Roma-Giannikou E, Karamolegou K, *et al.* Fiber intake and childhood appendicitis. *Int J Food Sci Nutr* 2000;51:153–7.
- 9 Johnson JR. Pathogenesis of acute appendicitis. *Br Med J* 1978;1:305.
- 10 Horton LW. Pathogenesis of acute appendicitis. *Br Med J* 1977;2:1672–3.
- 11 Burkitt DP. The aetiology of appendicitis. *Br J Surg* 1971;58:695–9.
- 12 Wei PL, Chen CS, Keller JJ, *et al.* Monthly variation in acute appendicitis incidence: a 10-year nationwide population-based study. *J Surg Res* 2012;178:670–6.
- 13 Zingone F, Sultan AA, Humes DJ, *et al.* Risk of acute appendicitis in and around pregnancy: a population-based cohort study from England. *Ann Surg* 2015;261:332–7.
- 14 Bundy DG, Byerley JS, Liles EA, *et al.* Does this child have appendicitis? *JAMA* 2007;298:438–51.
- 15 Rabah R. Pathology of the appendix in children: an institutional experience and review of the literature. *Pediatr Radiol* 2007;37:15–20.
- 16 Silen W. Acute appendicitis. *Harrison's principles of internal medicine*, 16th. New York: Mc Graw Hill, 2005:1805–8.
- 17 Carr NJ. The pathology of acute appendicitis. *Ann Diagn Pathol* 2000;4:46–58.
- 18 Alvarado A. A practical score for the early diagnosis of acute appendicitis. *Ann Emerg Med* 1986;15:557–64.
- 19 Ohle R, O'Reilly F, O'Brien KK, *et al.* The Alvarado score for predicting acute appendicitis: a systematic review. *BMC Med* 2011;9:139.
- 20 Downs TM. Congenital malformations of the appendix—a familial disease. *Ann Surg* 1942;115:21–4.
- 21 Baker EGS. A family pedigree for appendicitis. *J Hered* 1937;28:187–92.
- 22 Andersson N, Griffiths H, Murphy J, *et al.* Is appendicitis familial? *Br Med J* 1979;2:697–8.
- 23 Arnbjörnsson E. Acute appendicitis: a familial disease? *Curr Surg* 1982;39:18–20.
- 24 Duffy DL, Martin NG, Mathews JD. Appendectomy in Australian twins. *Am J Hum Genet* 1990;47:590–2.
- 25 Gurbuz AT, Muckleroy SK, Davis-Merritt D. Simultaneous acute appendicitis in monozygotic twins: coincidence or genetic? *Am Surg* 1996;62:407–8.
- 26 Oldmeadow C, Wood I, Mengersen K, *et al.* Investigation of the relationship between smoking and appendicitis in Australian twins. *Ann Epidemiol* 2008;18:631–6.
- 27 Sadr Azodi O, Andrén-Sandberg A, Larsson H. Genetic and environmental influences on the risk of acute appendicitis in twins. *Br J Surg* 2009;96:1336–40.
- 28 Nyboe Andersen N, Gørtz S, Frisch M, *et al.* Reduced risk of UC in families affected by appendicitis: a Danish national cohort study. *Gut* 2017;66:1398–402.
- 29 Gauderer MW, Crane MM, Green JA, *et al.* Acute appendicitis in children: the importance of family history. *J Pediatr Surg* 2001;36:1214–7.
- 30 Drescher MJ, Marcotte S, Grant R, *et al.* Family history is a predictor for appendicitis in adults in the emergency department. *West J Emerg Med* 2012;13:468–71.
- 31 Rivera-Chavez FA, Peters-Hybki DL, Barber RC, *et al.* Innate immunity genes influence the severity of acute appendicitis. *Ann Surg* 2004;240:269–77.
- 32 Basta M, Morton NE, Mulvihill JJ, *et al.* Inheritance of acute appendicitis: familial aggregation and evidence of polygenic transmission. *Am J Hum Genet* 1990;46:377–82.
- 33 Basta M, Radovanović Z, Radojčić C. On the association between appendicitis and ABO blood groups. *Transfusion* 1986;26:305–6.
- 34 Basta M, Radovanović Z, Radojčić C. Increased frequency of Rh(E) in acute appendicitis. *Hum Hered* 1987;37:384–6.
- 35 Kim K, Kim YH, Kim SY, *et al.* Low-dose abdominal CT for evaluating suspected appendicitis. *N Engl J Med* 2012;366:1596–605.

Copyright 2017 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow