

# Importance of Family History and Genetics for the Prediction of Acute Appendicitis

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## Abstract

Background: Although inflammatory disease of the vermiform appendix has been recognized as such for more than 100 years, its etiology remains a subject of controversy. The notion that appendicitis is familial, is not only important for understanding the etiology of the condition but might contribute substantially to the diagnosis and thus provide an indication for early surgical intervention.

Data Sources: An extensive Medline search, textbooks, scientific reports and scientific journals are the data sources.

Conclusions: Previous authors have developed clinical scores to predict appendicitis. The most popular one is Alvarado Score. If we add family history to this score, can we predict acute appendicitis?

## INTRODUCTION

Appendectomy is the most commonly performed emergency surgical procedure and accounts for 1-2% of all surgical operations<sup>1</sup>. Acute appendicitis occurs in 1/7 to 1/17 people<sup>2</sup>, mostly in adolescents and young adults. It has a life-time risk of 7%<sup>3</sup>. In the century since its recognition<sup>4</sup>, no progress has been made in elucidating its etiology and pathogenesis. According to the leading theory<sup>5</sup>, the initial event in the pathogenesis of acute appendicitis is obstruction of the lumen by factors like fecaliths, foreign bodies, intestinal parasites, tumors, or lymphoid follicular enlargement due to viral infections. However, obstructive elements have been identified in only 30%-40% of removed inflamed appendices<sup>6</sup>.

## FAMILY HISTORY

Firstly at 1937 Baker described a family pedigree in which 50% of the members were operated on for appendicitis<sup>7</sup>. Andersson et al.<sup>8</sup> and also Arnbjornsson<sup>9</sup> showed a high incidence of appendicitis among immediate family members. The familial tendency to acute appendicitis may perhaps be explained by environmental factors such as a specific bacterial infection, certain food habits<sup>8</sup>, or a genetic difference in resistance to bacterial infection<sup>7</sup>. Gauderer et al. suggested that children who have appendicitis are twice as likely to have a positive family history than are those with

right lower quadrant pain (but no appendicitis) and almost three times as likely to have a positive family history than are surgical controls (without abdominal pain)<sup>10</sup>. Brender et al. studied the family history of appendicitis in 135 children with histologic confirmation of acute appendicitis and in 212 control children without appendicitis, matched by age, sex and admission date. They found that parents of patients with appendicitis were approximately 10% more likely than parents of control children to have a positive history of this disease; in contrast, seven patients with appendicitis had siblings with a history of appendicitis, whereas only 0.64 would have been expected on the basis of the proportion among the control group; a significant positive trend was also noted between the proportion of family members with a history of appendicitis and risk for this disease in children. Finally they suggested that these results indicate some familial tendency for appendicitis<sup>11</sup>. Downs suggested another point in reviewing a family of 22 individuals in whom appendectomies had been performed: in 16 instances the appendix was found to be kinked at its base by a fibrous band. This peritoneal band might be inherited<sup>12</sup>. Although the presence of such a congenital malformation alone is not sufficient to precipitate an attack of acute appendicitis, it could well be considered as a predisposing factor in that it presents the mechanism by which the lumen of the appendix could be obstructed. Various anomalies of the appendix,

such as missing section of mesoappendix or morphological and anatomical variations including a coiled, short, long or retrocaecal appendix<sup>13,14,15</sup> described by many authors. Some authors also suggested that anatomical variations of the appendix might be inherited as a simple dominant unit-character.<sup>13, 15.</sup>

## TWINS

Twin studies are one of the important parts of the genetic based studies. Simultaneous cases of acute appendicitis are extremely rare<sup>16,17,18,19,20,21.</sup> All of the twins evaluated in the literature presented in the first or second decade within a day of each other. Although the South African twins presented slightly further apart, it is interesting that both were pyrexial and did not show leucocytosis<sup>21.</sup> Furthermore, both had their appendix in the retrocaecal position. There are not sufficient cases in the literature to conclude whether genetics or coincidence is responsible for this presentation.

## GENETICS

Genetic factors have been implicated in the etiology of acute appendicitis. Basta et al.<sup>22</sup> demonstrated a familial aggregation and polygenic transmission pattern in a retrospective analysis of families of 80 patients with appendicitis when compared to families of matched controls. They found the relative risk is 10.0 (4.7 - 21.4): in other words, the chance of appendicitis was 10 times greater in a child with at least one relative with reported appendectomy, compared with that in a child with no affected relatives. They also found that the proportion of relatives with appendicitis varied directly with the degree of relationship: 21% in first degree relatives (sibs, parents, and children), 12% in second degree relatives (grandparents, grandchildren, uncles, aunts, nieces, and nephews), and 7% in third degree relatives (first cousins). The complex segregation analysis supported a polygenic or multifactorial model with a total heritability of 56%<sup>22.</sup> This means that almost half of the variability in risk of acute appendicitis is due to random environmental factors. Basta et al. have further supported the hypothesis of familiarity of acute appendicitis and a possible polygenic mode of inheritance by demonstrating the association between appendicitis and ABO blood group<sup>23,</sup> and a probable linkage with the HLA system. They have found that blood group A have a much higher risk of having appendicitis than those of group O. They have also found that CcD-Ee Rh phenotype significantly more frequent in patients with appendicitis<sup>24.</sup> In the light of these studies, we can say that there can be a role of polygenic inheritance in acute appendicitis.

## CONCLUSION

The familial tendency to acute appendicitis may perhaps be explained by environmental factors such as a specific bacterial infection, certain food habits,<sup>8</sup> or a genetic difference in resistance to bacterial infection<sup>7.</sup> Although the presence of some congenital malformations alone is not sufficient to precipitate an attack of acute appendicitis, it could well be considered as a predisposing factor in that it presents the mechanism by which the lumen of the appendix could be obstructed. The complex segregation analysis supported a polygenic or multifactorial model with a total heritability of 56%<sup>22.</sup> This means that almost half of the variability in risk of acute appendicitis is due to random environmental factors.

Previous authors have developed clinical scores to predict appendicitis<sup>25, 26.</sup> The most popular one is Alvarado Score (table 1). If we add ABO blood type and family history to this score, can we predict acute appendicitis?

### Figure 1

Table 1: Alvarado scoring system

Sign/Symptom	Score
Migratory right iliac fossa pain	1
Anorexia	1
Vomiting/nausea	1
Temperature $\geq 37.3^{\circ}\text{C}$	1
Tenderness right lower quadrant	2
Percussion tenderness right iliac fossa	1
White cell count $\geq 10 \times 10^9/\text{L}$	2
Neutrophils $\geq 75\%$ or left shift	1
<b>Total</b>	<b>10</b>

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