Magnetic resonance imaging in acute appendicitis
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Chapter 1

General introduction and Outline of the thesis
General introduction

1.1 Background
A variety of acute conditions may affect the right lower quadrant (RLQ) prompting the patient to seek medical evaluation and possible therapy. Appendicitis is the most common cause of an acute abdomen with symptoms referred to the RLQ, particularly in young individuals [1]. However, abdominal symptoms and physical signs referring to the right lower quadrant may be caused by a variety of other conditions; “the mimickers of appendicitis” (e.g. cholecystitis, right sided colonic diverticulitis). Furthermore, the variable anatomical position of the appendix itself can mimic other clinical conditions as well, such as cholecystitis, sigmoid diverticulitis or gynecological conditions.

Imaging plays an ever more important role in refining the differential diagnostic considerations of appendicitis as most of these conditions can be diagnosed with Ultrasound (US), computed tomography (CT) or Magnetic Resonance Imaging (MRI), but the question is when, in which combination and with what objective. In this general introduction anatomy, pathophysiology, epidemiology, costs, diagnosis and treatment, will be discussed, focused on appendicitis and current imaging techniques.

1.2 Anatomy of the appendix
The vermiform appendix is located in the RLQ of the abdomen close to McBurney’s point [2, 3]. Its length varies from 2-20 cm, with an average length of 9cm [3, 4]. The attachment of the base of the appendix to the cecum is constant, whereas the tip can be found in a retrocecal, pelvic, subcecal, pre-ileal and post-ileal position [2, 3, 5]. The appendix may thus occupy various (moveable) positions: direct medially (37.6%), caudally (29.6%), laterally (6.8%) or retrocecaely (26%) [6]. Different pathologies of the cecum, particularly inflammation, may fix it in a particular position.
Identification of the normal position of appendix is important. This as in appendicitis various positions may produce different symptoms and signs related to the specific position, and can mimic other diseases [2, 7].

1.3 Pathophysiology of appendicitis

The term appendicitis covers four pathophysiological entities: acute appendicitis, chronic appendicitis, recurrent acute appendicitis and spontaneously resolving appendicitis. Chronic appendicitis is subject of many discussions, and most authors now conclude that there is no pathological substrate for chronic appendicitis [8, 9]. It therefore is beyond the scope of this study.

The etiology of acute appendicitis is obstruction of the lumen followed by infection [10]. Obstruction of the appendiceal lumen has been attributed to a number of etiologies including fecaliths, normal stool, viral induced ulcers, or lymphoid hyperplasia. Once this obstruction occurs the appendix becomes filled with mucus and distends, increasing intraluminal and intramural pressures, and when this pressure exceeds the venous pressure, vascular supply and lymphatic drainage become compromised exposing the appendiceal wall to bacterial invasion. This inflammation eventually extends through the submucosa to involve the muscular and serosal (peritoneal) layers, causing a localized peritonitis. Finally, the end-arteries supplying the appendix become thrombosed and the infarcted appendix becomes necrotic or gangrenous, an irreversible phase of appendicitis. This usually occurs at the distal end and the appendix begins to disintegrate. Perforation soon follows.
and fecally contaminated appendiceal contents spread into the peritoneal cavity. If the spilled contents are enveloped by omentum or adjacent small bowel, a localized abscess results; otherwise generalized peritonitis develops. The end result of this cascade is appendiceal rupture causing peritonitis, which may lead to septicemia and eventually death.

Spontaneously resolving appendicitis, recurrent acute appendicitis and acute appendicitis have the same etiology, pathophysiology and clinical symptomatology. In spontaneously resolving appendicitis the inflammatory process subsides in an early phase of the disease, however in recurrent appendicitis it recurs at a later moment in the patient's life. Spontaneously resolving appendicitis occurs in at least one in 13 cases of appendicitis and has an overall recurrence rate of 38%, with the majority of cases recurring within 1 year. [11-14].

1.4 Epidemiology and costs
Acute appendicitis is among the most frequent causes of surgical abdominal disease worldwide. The lifetime risk is 8.6% for males and 6.7% for females in the United States [1]. In 1997 in the United States, there were an estimated 252,682 appendicitis-related hospitalizations resulting in approximately one million hospital days and $3 billion in total of hospital charges [15]. In a study in Norway [16] the incidence of appendicitis and appendectomy from 1990 to 2001 was examined. Age-adjusted incidence rates for appendectomy were 117 per 100,000 for men and 116 per 100,000 for women. Incidence rates were highest among patients aged 10-29 years. In Ontario, Canada, between 1991-1998, the annual age and sex-adjusted incidence of acute appendicitis was 75 per 100,000 individuals, the incidence was highest in those aged 10-19 years. A significant seasonal effect was also observed, with the rate of acute appendicitis being higher in the summer months [17].

In Western Australia, from 1988 to 1997, emergency admission for appendectomy was the most common admission status and was more common in males than
females (122 v 103 per 100,000 person-years) [18]. In the only prospective study, in Norway, [19], the incidence of acute appendicitis during a 10-year period in a well defined population of 265,000 was analyzed. Between 1989 and 1998, 2,861 patients underwent surgery for suspected acute appendicitis. In 2,232 (78%) patients, acute appendicitis was confirmed histologically. Mean annual incidence was 84/100,000. In this prospective study, the incidence of acute appendicitis remained stable in a well-defined study population during the study period of 10 years.

In summary, acute appendicitis affects yearly about 1 per 1000 of the population and remains a disease that can affect anyone at any age. Several studies also suggest some seasonal effect, where appendicitis is more common in the summer months.

In the Netherlands the mean charges per patient for uncomplicated appendicitis related hospitalizations is about €4,000 [20]. If a conservative calculation about the annual costs of appendicitis related hospitalization in the Netherlands is made, with an incidence of 1 per 1000, in a population of about 16 million, average appendicitis related health care costs would be € 64 million[21].

1.5 Making the diagnosis of appendicitis
1.5.1 Clinical diagnosis
1.5.1.1 Symptomatic history
The classic history of acute appendicitis begins with poorly localized, central abdominal visceral pain; this results from smooth muscle spasm as a reaction to appendiceal obstruction. This is followed by anorexia, nausea and incidental vomiting. After a variable period of time that averages 6-12 hours, when the inflammation progress to the appendiceal wall to involve the parietal viscera which is somatically innervated, the pain shifts to the right lower quadrant and becomes localized[22]. The classic sequence of appendicitis is however encountered in less than half of patients and may also occur in other clinical conditions mimicking appendicitis. When
the process progresses the pain becomes more severe and causes discomfort on walking, moving and coughing. Often a feeling of constipation is experienced. Once an appendiceal phlegmon is formed the symptoms usually subside gradually.

When perforation occurs, an incidental, short relief of pain may be experienced. As a rule however pain gradually increases and becomes more severe and diffuse. Depending on the perforation being free or walled-off, symptoms of spreading peritonitis or abscess formation will become more noticable.

1.5.1.2 Physical examination

The most frequent physical finding of acute appendicitis is a localized tenderness on abdominal palpation around the location of the appendix, which is usually at or near McBurney’s point [2, 3]. This point roughly corresponds to the most common location of the base of the appendix where it is attached to the cecum. Other signs are direct and indirect rebound tenderness, pain on percussion, muscle guarding, cutaneous hyperesthesia, pelvic tenderness on the right side on rectal examination, and the presence of the psoas sign. Body temperature varies from normal to 38°C but may be higher.

1.5.1.3 Laboratory findings

Laboratory tests may be helpful in diagnosing appendicitis, but are usually of limited value. White blood cell count in early appendicitis is commonly elevated and shows a shift to the left. Sedimentation rate (ESR) is normal in the acute phase, and elevation of ESR may indicate progress of the inflammatory process. C-reactive protein (CRP) is usually elevated. Urine analysis is usually normal, however some protein, white and red blood cells are present in a significant number of patients [23]. Abnormal laboratory findings cannot reliably deliver a diagnosis of acute appendicitis. However, acute appendicitis is very unlikely when leukocyte count, neutrophile percentage and CRP level are simultaneously normal [22, 24].
1.5.2 The role of imaging

The clinical presentation of appendicitis is thus often confusing and problems may arise when symptomatic history and physical examination are unreliable or atypical. The symptomatic history may be unreliable especially in infants, mentally impaired patients or when a language and/or cultural barrier is present. Physical examination may be unreliable in patients who are obese or who have congenital or acquired malformations that affect anatomical locations. [25].

But even in patients with a clinically high suspicion of having appendicitis, the diagnosis is incorrect in a large number of patients. Rettenbacher et al. [26], showed that in patients with clinically high probability of having appendicitis, 65% actually had appendicitis (94 of 144 patients), 18% had an alternative diagnosis (26 of 144 patients), and 17% had no specific diagnosis (24 of 144 patients).

For almost two decades imaging has been increasingly used in the evaluation of patients clinically suspected of having appendicitis. The cornerstone of diagnosing appendicitis, with any imaging technique, is detecting a thickened appendix with a diameter of 7mm or more and with signs of periappendicitis, whereas the most reliable sign of excluding appendicitis is the visualization of a normal appendix [27].

1.5.2.1 Plain abdominal films

In patients with right lower quadrant pain, plain-film radiography is often non-specific and noncontributing.[28]. An appendiceal fecolith (appendicolith) may occasionally be found in asymptomatic individuals, but in patients with right lower quadrant pain its presence is suggestive of acute appendicitis [29-31]. Free peritoneal air in perforated appendicitis may occur but is very rare [32].

1.5.2.2 US

In the last two decennia numerous studies have shown the reliability of US in excluding or confirming the diagnosis acute appendicitis. It has been reported that
when patients suspected of appendicitis are examined by experienced operators, the sensitivity is 76-91%, specificity 74-100%, positive predictive value (PPV) 71-95% and negative predictive value (NPV) 76-98% [33-40]. In these studies non-vizualization of the appendix by US in cases of surgically proven appendicitis is deemed as false-negatives test results, although in these cases appendicitis can not be ruled out by US. Some false-positive results were those cases, where US showed appendicitis, but were symptoms resolved and no surgery was performed, although these cases could have been due to spontaneously resolving appendicitis.

In the early years the emphasis was on showing the inflamed appendix or an alternative diagnosis. When no appendix could be visualized, nor an alternative diagnosis, appendicitis could not be ruled out, and this was one of the disadvantages in the “early” era of US.

With newer US equipment, the normal appendix can be visualized more often and thus appendicitis be ruled out. It is often argued that US is too operator dependent for the referring physician to rely on. As US equipment is improving and experience is gained, also as part of residency training, in evaluation of patients with abdominal symptoms, one can argue whether this argument is valid. In a recent prospective study comparing US and CT in patients clinically suspected of having appendicitis, there was no significant difference in diagnostic accuracy between US and CT or between groups of radiologists, regardless of patient age, sex, or body mass index respectively [35]. Major advantages of US are widespread availability, low costs and lack of radiation.

1.5.2.3 CT
Many studies have shown the added value of CT in patients suspected of appendicitis. CT has impressive values above 90% for specificity, sensitivity, PPV and NPV for detecting and excluding appendicitis [33, 35-37, 41-43]. It is cost-effective in the evaluation of patients with RLQ pain [43, 44]. With modern CT scanners, the
scanning time is ultrafast, allowing for less motion artifacts; the resolution is isotropic resulting in multiplanar reformatting without loss of resolution. As a result the values mentioned above are above 95% [45].

The major disadvantage of CT scanning is the use of radiation, which cannot be ruled out as a risk factor for the general population. A typical dose for an abdominal CT examination is in the order of 10-15mSv [46], this means that one CT examination carries more radiation risk than 500 chest radiographs. An effective dose of 10mSv corresponds to an excess risk of radiation-induced cancer for a 25-year-old of about 1 in 900. The risk of fatal cancer induction is about 1 in 1800 [46-49]. The routine use of diagnostic CT examinations for benign diseases, as in appendicitis, must give rise to question whether the diagnosis can be obtained by other radiological means. This is especially the case in pregnant women and in young patients [50]. The International Commission on Radiological Protection (ICRP) recently published a report on radiation and pregnancy. This recommended, that if the expected dose for the fetus is high, as in abdominal or pelvic CT, one should question if the diagnosis could be obtained without the use of ionizing radiation [50, 51].
1.5.2.4 MRI

In the last decade MRI has emerged as a useful imaging modality for the evaluation of the gastrointestinal tract [52, 53]. Major advantages over CT are the lack of ionizing radiation and the higher intrinsic contrast resolution. Initially the MRI techniques were relative slow, preventing abdominal MRI in acute settings. However, the introduction of rapid sequences and improved hardware have led to sequences visualizing the entire abdomen in one breath hold. This has paved the way for MRI in acute diseases. MRI is gradually being introduced as a complementary imaging modality to CT in the diagnosis of patients with abdominal pain [53-61].

There are no known biological risks associated with MRI, even with high magnetic fields in laboratory settings in animal studies. To our knowledge, no delayed sequelae from undergoing or performing MRI examinations have been encountered, and it is expected that the risk of delayed sequelae is extremely small. The risk of exposing the developing fetus to any radiologic diagnostic imaging technique that uses ionizing radiation is probably greater than the theoretical risk of MRI. According to the Safety Committee of the Society for Magnetic Resonance Imaging, MRI is indicated for use in pregnant women when the result of nonionizing diagnostic imaging is inadequate, such as US, for diagnosis or when MRI is expected to provide important information for proper treatment of the fetus or mother [62, 63].

MRI of the abdomen does not routinely require contrast material, thus minimizing patient discomfort and possible systemic adverse reactions, whereas CT often requires intravenous, rectal or oral contrast material.

A frequently encountered problem of MR is the availability especially out of hours. Other limitations of MR imaging include poorer spatial resolution compared with that of CT, increased sensitivity to motion-related artifacts, and limited compatibility with equipment used in intensive care and monitoring of patients. CT is many times faster than MR imaging, even when the latter is performed with fast gradient-echo sequences, and therefore CT is more suitable for diagnostic imaging of an acutely
ill patient, who may be unable to cooperate and lie still for the duration of MR image acquisition. Finally, most radiologists are more familiar with the appearance of acute abdominal and pelvic conditions on CT scans than they are with the MR imaging features.

25-year-old woman clinically suspected of appendicitis. US was equivocal due to a deep pelvic position of the appendix. Coronal T2-weighted (a), and transverse T2 (b) and T2-fatsuppression (c) weighted images show a 14 mm enlarged appendix (arrow) with an appendicolith at its base. Surgery and pathology revealed phlegmonous and hemorrhagic appendicitis without perforation.

1.5.2.5 The effects of imaging on the use of hospital resources
In a landmark study by Rao et al [43], it was shown that routine appendiceal CT performed in patients who present with suspected appendicitis improves patient care and reduces the use of hospital resources. It has also been argued that the use of US as a primary imaging modality would be even more cost-effective [64].
1.6 Goals of Treatment: the false-positive clinical diagnosis (or negative laparotomy rate), the false-negative clinical diagnosis and perforation rate

The negative laparotomy rate reflects the number of false positive diagnoses. The false-negative clinical diagnosis is reflected by the perforation rate. The perforation rate is defined as the number of perforated appendices divided by the total number of acutely inflamed appendices that are removed as an emergency procedure. Perforation is defined as a per-operatively confined, macroscopical defect in the appendiceal wall and/or the presence of pus or feces in the abdominal cavity[9].

Surgeons tend to favor early surgery in an attempt to avoid perforation of the appendix but this results in a number of unwarranted operations. This is accepted practice, in an attempt to reduce morbidity and mortality from perforated appendicitis. Diagnostic accuracy may be increased by a conservative attitude to surgery in uncertain cases.[65] This strategy is criticized, however, for giving an increased perforation rate. The perforation rate does not only reflect hospital or surgeons delay alone, but more important patient’s delay and family doctor’s delay[66, 67]. Walled-off perforations with development of an appendiceal mass usually will be treated conservatively, so no confirmation of the diagnosis in these patients is obtained. Almost all studies on diagnostic accuracy deliberately leave out patients with an appendiceal mass and deal only with the results of emergency appendectomy. This implies that the actual perforation rate is could be much higher than reported in these studies. In others, the diagnosis of appendicitis can be overestimated clinically at surgery, because histological confirmation is not always present or accurate, and this can influence the calculated perforation rate [68]. The pathological criteria for acute appendicitis is the presence of polymorphic granulocytes throughout the appendiceal wall including the muscularis [9]. All other pathologic diagnoses such as chronic fibrosis, parasitic infestation, coprostasis are considered as normal. The natural course of non-perforating appendicitis is not known. Many surgeons regard
acute appendicitis as a progressive inflammation, but spontaneous resolution may occur [69, 70] and microscopy of excised appendices may show signs of healed inflammation. A high rate of exploratory laparotomy in suspected appendicitis increases the number of confirmed cases [71], presumably by adding cases of self limiting inflammation which otherwise would have escaped detection. Inflammation without symptoms, which is seen in up to 35% of incidentally removed appendixes [72], may also be erroneously diagnosed at laparotomy as appendicitis. The observed incidence of non-perforating appendicitis will therefore be influenced by a willingness to perform exploratory laparotomy in cases of suspected appendicitis.

1.7 Influence of imaging on negative laparotomy rate, and perforation rate in appendicitis

In a study by Raman et al.[73] the annual rate of use of preoperative helical CT among patients who underwent surgery for suspected acute appendicitis increased from 20% in 1996 to 85% in 2006, and, the overall rate of false positive diagnosis of appendicitis among adults decreased significantly, from 24% to 3%. The overall rate of pathologically proven appendiceal perforation decreased significantly, from 18% in 1996 to 5% in 2006.

One could state that an increase in pre-operative imaging in patients suspected of appendicitis can significantly lower the negative appendectomy rate or misdiagnosis [74-76]. However, some difficulties are encountered in making this assumption. First, in hospitals where diagnostic laparoscopies are performed in patients suspected of appendicitis and where a normal appendix is encountered and left in situ, low negative appendectomy rates in combination with low pre-operative imaging rates can be the result. Secondly, when imaging is performed after selection of the patients to confirm true negatives. In this way the use of imaging is not increased in patients who actually had appendicitis, but the number of negative appendectomies decreases. Critics will argue that imaging has not caused the lower negative appendectomy rate.

Besides the negative appendectomy rate, pre-operative imaging is not only about
detecting a normal or inflamed appendix, but also about detecting a substantial number of alternative diagnoses.

As this thesis concerns MRI in appendicitis, one needs to be aware of the various factors that can influence perforation rate and negative laparotomy as discussed above, in order to be able to draw conclusions concerning the beneficial effect of imaging on these parameters.

Outline of the thesis

Trans-abdominal ultrasound (US) and abdominal computed tomography (CT) have proven to be reliable procedures in detecting or excluding appendicitis and these imaging modalities are widely available in the Netherlands, but are these modalities actually being used in this group of patients? In chapter 2 a survey among all Dutch hospitals is described concerning the current use of pre-operative radiologic imaging. The purpose of the study in chapter 3 was to determine the sensitivity and specificity of MRI in detecting or excluding appendicitis in patients clinically suspected of appendicitis; the effect on outcome of appendectomy and the effect of imaging strategies on the use of hospital resources were determined. When US results are equivocal in patients suspected of appendicitis, an adjunctive abdominal CT is often performed to rule out appendicitis, but how does MRI perform in such circumstances? In chapter 4 the role of adjunctive abdominal MRI in patients suspected for appendicitis is investigated, when US results are equivocal. Chapter 5 provides an image based differential diagnosis of acute appendicitis with emphasis on abdominal MRI. Pregnant patients are an important group of patients in whom an abdominal CT is preferably not used because of radiation exposure. Chapter 6 describes the MRI results in a group of pregnant patients, clinically suspected of appendicitis. In chapter 7 and 8 abdominal MRI results of possible mimickers of appendicitis, namely cecal diverticulitis and omental infarction are presented respectively. Chapter 9 presents the summary and conclusions.
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