J Ultrasound (2015) 18:317–320
DOI 10.1007/s40477-015-0176-z

REVIEW ARTICLE

Acute acalculous cholecystitis and cardiovascular disease: a land of confusion

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Received: 25 March 2015 / Accepted: 22 June 2015 / Published online: 26 July 2015

Abstract Acute acalculous cholecystitis (AAC) can be defined as acute inflammatory disease of the gallbladder without evidence of gallstones. The first case was reported in 1844 by Duncan et al.; however, some cases may have been missed previously in view of the complexity of the diagnosis. Several risk factors have been identified, and cardiovascular disease (CVD), in view of its multiple mechanisms of action, seems to play a key role. Atypical clinical onset, paucity of symptoms, overlap with comorbidities, and lack of robust, controlled trials result often in under or misdiagnosed cases. Moreover, laboratory results may be negative or not specific in the late stage of the disease, when a surgical treatment cannot be longer helpful if complications arise. A rapid diagnosis is therefore essential to achieve a prompt treatment and to avoid further clinical deterioration. In this short review, we would present the current evidence regarding epidemiology, pathophysiology, and clinical presentation of the complex relation between AAC and CVD. Then, we fully emphasize the role of ultrasound to achieve an early diagnosis and an appropriate treatment in suspected cases, reducing mortality and complications rates.

Keywords Acute acalculous cholecystitis · Gallbladder · Cardiovascular disease · Ultrasonography · Emergency Department · Surgery

Riassunto La colecistite acuta alitiasica (AAC) può essere definita come una infiammazione acuta della colecisti in assenza di calcoli. Uno dei primi casi clinici riportati in letteratura risale al 1844 (Duncan et al.) ma verosimilmente alcuni di questi sono passati inosservati a causa della complessitá del percorso diagnostico. Numerosi fattori di rischio sono stati identificati e, tra questi, le malattie cardiovascolari, in considerazione di diversi meccanismi d'azione, sembrano assumere una posizione importante e giocare un ruolo chiave. Molti casi possono passare inosservati per varie ragioni che vanno dall'esordio clinico atipico, la povertá di sintomi, la sovrapposizione clinica e strumentale con altre comorbiditá, la carenza di trial controllati. Inoltre i test di laboratorio possono risultare negativi o non specifici anche negli stadi avanzati della malattia, quando la terapia chirurgica può non rivelarsi più utile in caso di complicanze. Una diagnosi rapida é dunque necessaria per instaurare un trattamento mirato e per evitare un ulteriore deterioramento clinico. In questa breve revisione vogliamo mettere in risalto le evidenze attuali che riguardano l'epidemiologia, la fisiopatologia e la presentazione clinica della complessa relazione esistente tra le malattie cardiovascolari e la colecistite acuta alitiasica. Il nostro intento é dunque quello di enfatizzare il ruolo dell'ultrasonografia nel raggiungimento, nei casi sospetti, di una diagnosi precoce e di un trattamento appropriato, al fine di ridurre il tasso di complicanze e la mortalitá.

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Abbreviations

AAC	Acute acalculous cholecystitis
US	Ultrasound scan
CT	Computed tomography
ED	Emergency Department
EKG	Electrocardiogram
AMI	Acute myocardial infarction
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
CVD	Cardiovascular disease

Introduction

Acute acalculous cholecystitis (AAC) can be defined as an acute inflammatory disease of the gallbladder in the absence of cholelitiasis [1]. One of the first reported cases dates back to 1844 [2] but the diagnosis remains difficult for many reasons: complexity of clinical onset, paucity of symptoms, lack of controlled trials and clinical overlap with other conditions such as cardiovascular disease (CVD) [1].

Multifactorial pathogenesis

AAC consists in gallbladder inflammation with multifactorial pathogenesis [1, 3, 4] and is complicated by high morbidity and mortality [5, 6]. It is often associated with severe conditions [1] and occurs commonly in hospitalized and critically ill patients due to multiple causes that are summarized in two main mechanisms: ischemia and bile stasis [1, 7]. Various types of shock and hypovolemia, heart failure, myocardial ischemia, dehydration may lead to low-flow state with subsequent gallbladder ischemia and inflammation [8, 9]. Other causes of local ischemia may include diabetes mellitus, abdominal vasculitis, malignant disease [8, 9], cholesterol embolization [9] and sepsis with visceral arterial hypoperfusion [6]. Moreover, concentration of biliar salts and bile stasis can be the result of fever, absence of oral feedings, and dehydration. The most common complications are represented by empyema, gangrene, and perforation, and they occur in 6–82 % of cases [1, 7].

Epidemiology

Acalculous cholecystitis represents 2–15 % of all acute cholecystitis, with a mean of 10 % and a mild predominance in male about 60 years of age [1]. Conversely, calculous cholecystitis occurs more frequently in women over 50 years [10, 11]. AAC arises in 0.2–0.4 % of all critical ill patients and mortality ranges from 10 to 90 % with an average of 30 % [1] in opposite to 1 % of calculous cholecystitis [12]. The risk of death is directly related to a delayed diagnosis [1], and an early diagnosis and treatment leads to a clinical improvement and better outcomes [3, 4].

From CVD to acute cholecystitis

Gastrointestinal disorders and cardiac events are strictly correlated: these conditions often coexist and the differential diagnosis can result very difficult [13]. As mentioned above, the cardiovascular disorders that are associated with an hypovolemic state, such as acute myocardial infarction (AMI) or acute heart failure (AHF) [8, 9, 14, 15], can result in ischemic damage of the gallbladder and its inflammation. Sogutlu G et al. reported a case of AAC induced by aortic dissection Bakey type III, hypothesizing pathogenesis mechanisms as bile stasis, sepsis, and ischemia [16]. In addition, Roth et al. reported a case of AAC complicating aortic dissection Bakey type III in a 57-year-old man, postulating a multifactorial etiology at the origin of the disorder [17].

Moreover, the treatment of some cardiovascular disorders itself may contribute to the pathogenesis: several cases of acalculous cholecystitis following coronary artery bypass [18] or cardiovascular surgery [19, 20] in cardiopathic patients are reported in the literature. Mastoraki et al. have further highlighted this correlation: biliary complications occurred in 14 of 4588 patients who underwent open heart surgery, after exclusion of those with presurgical hepatobiliary disorders [21].

Acute cholecystitis and CVD

In 1986, Krasna et al. suggested that angina pectoris, arrhythmias, non-specific ST-T waves on electrocardiogram (ECG) may be associated with acute cholecystitis or biliary colic, and hypothesized a vagally mediated reflex mechanism. The same authors emphasized the difficulty of differential diagnosis due to symptoms overlapping and the importance of an early diagnosis and treatment: a delay in treatment while awaiting cardiac biomarkers may lead to serious complications [22]. Acute cholecystitis has been often associated with troponinosis [23] and rise in CPK [24]; moreover, some patients experienced retrosternal pain and ST changes on ECG [25] in association with gallbladder disease. Gallbladder disease has been often associated with conduction disturbances, as reported by Franzen et al., who documented the case of 48-year-old-woman who has suffered from acute cholecystitis followed by two syncopal episodes. Serial ECG revealed third

degree atrioventricular block, but, after surgical removal of gallbladder, electrophysiological testing, ECG at rest and after exercise, carotid sinus massage, echocardiography, and coronary angiography were all negative [26]. In opposite, Valentin et al. reported three episodes of asystolic cardiac arrest during surgical manipulation in a 70-year-old man without cardiovascular or ischemic heart history. Laparoscopic cholecystectomy was successfully performed only after insertion of a provisional pacemaker [27]. An episode of asystolia complicated acalculous cholecystitis in a case described by Lau YM et al. [28]. The authors revisited the Cope's sign and reflex bradicardia, that was previously described on British Medical Journal by O'Reilly and Krauthamer [29] in two patients, the first with cholelithiasis and acute necrotizing cholecystitis, and the second with hemorrhagic cholecystitis.

Some authors have suggested that troponinosis and ST changes may be due to acute cholecystitis and not only related to myocardial ischemia or any other acuteness (as proved by further investigations). Demarchi MS et al. supported that this concern should be ponderated when evaluating patients with analog clinical presentation [30].

Cerebrovascular disease

As a further evidence that acalculous cholecystitis may be the end result of several pathophysiological mechanisms, Ushiyama et al. [31] described an 1 % incidence of acute AAC in cerebrovascular patients, with a mean time to clinical onset from cerebrovascular disease of 25 days and of 5.8 days after the beginning of oral or tube food intake. Most common clinical onset was represented by fever (70 %) in opposite to abdominal pain which occurred in 20 % of patients. 8/10 patients were male. Elevated CRPs, leukocytosis (60 %), and elevated aminotransferase (30 %) occurred frequently. The multifactorial etiology was probably related to fasting, arteriosclerosis, and enhanced bile concentration; the authors stressed the concept that ACC is difficult to diagnose but can be a considerable complication that can take place during acute phase of patients with cerebrovascular disease. The concern that cerebrovascular disorders may have an important role for the gallbladder disease through different risk factor was advanced by Tomás et al. too [32].

Conclusion

Diagnostic confusion

The diagnosis of AAC remains difficult to achieve: many authors stressed the symptom overlapping with concomitant disorders, such as CVD. Patients often are asymptomatic, or clinical status and examination cannot be diriment. Moreover, laboratory data may be entirely negative, not helpful or mild positive and aspecific in late stages of the disease, when the treatment may be ineffective, not helpful or impracticable. An early diagnosis and treatment can be useful, or, in certain cases, lifesaving.

Role of ultrasonography

In this land of confusion, ultrasound (US) plays a key role in the AAC diagnosis: it allows a rapid diagnosis, is simple, cost-saving, safe, and radiation-free. Because of its accessibility and portability, US represents an useful diagnostic tool in the Emergency Department (ED) not only for acute gallbladder disease, but also for other conditions causing abdominal pain, becoming fundamental in the clinical practice. Computed tomography (CT) add further details when US is not clear, while hepatobiliary scintigraphy, although has got a high diagnostic accuracy, represents a slow diagnostic tool during the diagnostic work-up in the ED [33]. Many authors tried to establish useful US criteria to allow a correct AAC diagnosis: ultrasonography major diagnostic criteria for gallbladder inflammation are represented by wall thickness, subserosal edema or pericholecystic fluid, and intramural gas. Hydrops and sludge are minor criteria. The triad composed by thickness, hydrops, and sludge is the one preferred for diagnosis [34–39].

In conclusion, a high index of suspicion, along with an appropriate history, clinical findings, and laboratory data are needed to achieve a correct and rapid diagnosis, but they should be completed by ultrasonography, because a proper diagnosis allows an early treatment of AAC, that reduces the risk of mortality and complications rate [40, 41].

Compliance with ethical standards

Conflict of interest None.

Ethical standards The study was in accordance with the ethical principles of the Declaration of Helsinki.

Informed consent For this type of study, formal consent is not required.

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