Role of Helicobacter pylori in pathogenesis of post ERCP pancreatitis

Thesis

Submitted for Partial Fulfillment of M.D Degree
in ***Internal Medicine***

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2015

Acknowledgement

Thanks first and last to ***God*** *as we owe to him for his great care, support and guidance in every step in our life.*

I would like to express my sincere gratitude to ***Prof. Dr. Khaled Hamdy Abdel Mageed****, Professor of Internal Medicine, Faculty of Medicine, Ain Shams University who has so kindly supervised my thesis, I am deeply grateful to him for his professional advice, his guidance and support.*

I wish also to express my gratitude to ***Dr. Marcel William Keddeas****, Assistant Professor of Internal Medicine, Faculty of Medicine, Ain Shams University under her supervision and kind advice, I had the honor to complete this work.*

I am also grateful to ***Dr. Zainab Ahmed Ali El-din,*** *Assistant Professor of Internal Medicine, Faculty of Medicine, Ain Shams University for her guidance, continuous assistance and sincere supervision of this work.*

I would like also to express my sincere appreciation and gratitude to ***Dr. Sameh Ahmed Abdel Bary****, Assistant Professor of Internal Medicine, Faculty of Medicine, Ain Shams University for his continuous directions and support throughout the whole work.*

I am also greatly indebted to ***Dr. Eslam Safwat Mohammed,*** *Lecturer of Internal Medicine, Faculty of Medicine, Ain Shams University for his enthusiasm and help.*

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List of Abbreviations

AIP : Autoimmune pancreatitis.
AlpA/B : Adherence-associated lipoprotein A and B.
AP : Acute pancreatitis.
ASPP2 : Apoptosis-stimulating Protein of p53-2.
BabA : Blood-group-antigen-binding adhesion.
Bid : twice a day.
BMI : Body mass index.
CA : Carbonic anhydrase.
CAC : Coronary artery calcification.
CAD : Coronary heart disease.
Cag A : Cytotoxin associated gene A.
Cag-PAI : Cag pathogenicity island .
CECT : Contrast enhanced CT- scan.
CFTR : Cystic fibrosis trans-membrane conductance regulator gene.
CGRP : Calcitonin gene-related peptide.
CNS : Central nervous system.
COX2 : Cyclooxygenase-2.
CRH : Corticotropin-releasing hormone.
CT : Computed tomography.
CT FNA : Computed tomography guided fine needle aspiration.
EGFR : Epidermal growth factor receptor.
ERCP : Endoscopic retrograde cholangiopancreatography.
ESGE : European Society of Gastrointestinal Endoscopy.
EUS : Enoscopic ultrasound.
Fr : French.
GABA : γaminobutiric acid.
GGT : γ-glutamyl transpeptidase.
GH : Growth hormone.
GHIH : Growth hormone inhibiting hormone.

List of Abbreviations *(Cont.)*

GHRH : Growth hormone-releasing hormone.
GIP : Gastric inhibitory polypeptide.
GIS : Gastrointestinal immune system.
GLP : Glucagon like peptides.
H. pylori : Helicobacter pylori.
HP-NAP : H. pylori neutrophil-activating protein.
HPSA : Helicobacter Pylori stool antigen.
HtrA : High temperature requirement A.
IHD : Ischemic heart disease.
ILs : Interleukins.
ITP : Idiopathic thrombocytopenic purpura.
ITT : Intention-to-treat.
LPS : Lipopolysaccharides.
MALT : Mucosa-associated lymphoid tissue.
MHE : Minimal hepatic encephalopathy.
MODS : Multiple organ dysfunction syndrome.
MRCP : Magnetic resonance cholangio-pancreatography.
MRI : Magnetic resonance imaging.
NG : Nitroglycerin.
NPV : Negative predictive value.
NSAID : Non steroidal anti-inflammatory drugs.
OipA : Outer inflammatory protein A.
OMP : Outer membrane proteins.
PAI : Pathogenicity island.
PBP : Pylori plasminogen binding protein.
PCR : Polymerase chain reaction.
pDCs : Plasmacytoid dendritic cells.
PDE : Phosphodiesterase.
PDE-5 : Phosphodiesterase type 5

List of Abbreviations *(Cont.)*

PEP : Post-ERCP pancreatitis.
PLA2 : Phospholipase-A2.
PP : Per-protocol.
PPI : Proton pump inhibitor.
PPV : Positive predictive value.
RCTs : Randomized controlled trials.
ROC : Receiver operator characteristic curve.
RUT : Rapid urease test.
SabA : Sialic acid-binding adhesin.
SIRS : Systemic inflammatory response syndrome.
sLeX & sLea: Sialyl-Lewis x/a.
SOD : Sphincter of Oddi dysfunction.
SPINK1 : Serine protease inhibitor Kazal type 1.
SRIF : Somatotropin release inhibiting factor.
SSA : Species-specific antigen.
SSc : Systemic sclerosis.
SST : Somatostatin.
T4SS : Type IV secretion system.
TEER : Trans-epithelial electric resistance.
TNF : Tumor necrosis factor.
TSH : Thyrotropin.
UBR2 : Ubiquitin-protein ligase E3 component n-recognin 2.
UBT : Urea breath test.
VacA : Vacuolating cytotoxin.
VIP : Vasoactive intestinal peptide.

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Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) is an important invasive procedure used in managing a diverse group of pancreatic and biliary disorders. The most common serious adverse event is post-ERCP pancreatitis (PEP) ***(Artifon et al., 2010).***

Acute pancreatitis remains the most common complication of ERCP, with an incidence ranging from 2% - 4% in low risk patients to 8% - 20% in those at high risk and an overall average risk of approximately 10% ***(Katsinelos et al., 2012).***

The pathophysiology of PEP is not well understood. Mechanical, hydrostatic, chemical, enzymatic, allergic, thermal, cytokine and microbiological factors have all been proposed as causes. Many studies suggest that PEP results from mechanical trauma with injury of the papilla or pancreatic sphincter causing swelling of the pancreatic duct and obstruction to the flow of pancreatic enzymes. This hypothesis remains controversial and no consensus related to the pathogenesis of PEP has been established ***(Woods & Willingham, 2010).***

The decreased production and release of somatostatin play also an important role in pancreatitis. This is caused by

a decreased count of D cells in the antrum, the activation of H3 receptors on D cells due to N alpha-methyl histamine production by Helicobacter pylori. After effective bacterium eradication, D cell counts increase significantly ***(Maciorkowska et al., 2006).***

PEP was diagnosed when new-onset or increased abdominal pain lasting more than 24 hours caused an unplanned admission of an outpatient for more than one night or prolonged hospitalization of an inpatient and was associated with an at least threefold increase in serum amylase, at approximately 6 or 24 hours post-procedure ***(Katsinelos et al., 2012).***

Severe complications of ERCP have decreased significantly during recent years due to technical advances and accumulating experience of the physicians. However, the incidence of PEP has remained constant and has become a major concern. Several mechanical and pharmacological interventions have been used to prevent PEP ***(Zhang et al., 2009).***

Several drugs have been used to prevent post-ERCP pancreatitis, but their results are controversial. The drugs included in randomized controlled studies were somatostatin and its analog octreotide, steroids, nifedipine, interleukin-10, allopurinol and gabexate ***(Chan et al., 2008).***

Among these, somatostatin and gabexate have shown some promises. A meta-analysis indicated that somatostatin given as an infusion for 12 h or as a bolus could reduce the rate of pancreatitis and hyper-amylasemia after ERCP, but given as an infusion for less than 12 h could not prevent PEP ***(Rudin et al., 2007).*** However, another study concluded that short-term or long-term infusion of somatostatin and gabexate proved ineffective in reducing PEP ***(Andriulli et al., 2007).***

The possible reasons for why somatostatin can prevent acute pancreatitis are related to the effects of inhibiting pancreatic exocrine secretion by suppressing the release of secretin and cholecystokinin and reducing the pressure in the intra-pancreatic ducts by inhibiting the motility of the sphincter of Oddi ***(Chan et al., 2008).***

Somatostatin can modulate the immune inflammatory response and the degree of severe acute pancreatitis through the apoptosis and adhesion of leukocytes ***(Tang et al., 2007).*** Moreover, somatostatin dose-dependently inhibits TNF-α-induced IL-6 secretion, and some of the therapeutic actions of somatostatin on acute pancreatitis may be mediated by the reduction of local IL-6 secretion in the pancreas ***(Katsinelos et al., 2012).***

Yet, the association between Helicobacter Pylori infection and somatostatin deficiency and its relation with occurrence of post ERCP pancreatitis is still controversial.

Aim of the Work

The aim of this work is to identify the role of Helicobacter pylori infection in the pathogenesis of post ERCP pancreatitis.

Post ERCP Pancreatitis
Acute Pancreatitis

Definition:

Acute pancreatitis (AP), defined as the acute nonbacterial inflammatory condition of the pancreas, is derived from the early activation of digestive enzymes found inside the acinar cells, with variable compromise of the gland itself, nearby tissues and other organs. AP is a disease with extremely different clinical expressions.

Most patients suffer a mild and limited disease but about one fifth of cases develop multiple organ dysfunction syndrome (MODS), accompanied by high mortality ***(Thoeni, 2012).***

Causes of acute pancreatitis:

- Toxic- Metabolic:
  - Alcohol
  - Hypertriglyceridemia, hypercalcemia
  - Drugs and pills e.g: Azathioprine, thiazides, NSAIDs, steroids.
  - Organophosphorus and other toxic substances
  - Venoms (scorpion, spiders)

- Mechanical:
  - Biliary: lithiasis, microlithiasis, sludge

- Congenital malformations
  - Pancreas divisum
  - Annular pancreas
- Anatomical variants:
  - Duodenal duplication
  - Duodenal diverticulum
  - Choledochal cyst
- Ampullary dysfunction stenosis
- Trauma: Post ERCP pancreatitis

- Genetic:
  - Familial (hereditary pancreatitis).
  - Sporadic
- Miscellaneous:
  - Vascular
    - Hypotension
    - Vasculitis
    - Embolisms
    - Hypercoagulability
  - Autoimmune
    - Sjögren syndrome
    - Primary sclerosing cholangitis
    - Celiac disease
    - Autoimmune hepatitis