INTRODUCTION

Chronic liver disease in the clinical context is a disease process of the liver that involves a process of progressive destruction and regeneration of the liver parenchyma leading to fibrosis and cirrhosis ***(Feranchak et al., 2001)***.

Chronic liver disease encompasses a wide spectrum of disorders, including infections, metabolic, genetic, idiopathic and autoimmune disease. The patient with chronic liver disease have on increased incidence of infections especially pneumonia such patient have many defect in host defenses ***(Mews and Sinatra, 1993).***

The pediatric chronic liver disease is categorized as Anatomic abnormalities which are subdivided into intrahepatic bile duct disease as congenital hepatic fibrosis, int rahepatic paucity of bile ducts and caroli's disease and extrahepatic bile duct disease as extrahepatic biliary atresia, choledochal cyst…..etc . Infectious causes as HBV, HCV, HDV….etc. Inherited metabolic liver disease as cystic fibrosis, glycogen storage disease, Wilson's disease ….etc. autoimmune as autoimmune chronic hepatitis, primary biliary cirrhosis **(Kamil *et al, 2002).***

Streptococcus pneumonia is important cause of morbidity and mortality in persons of all ages worldwide ***(Pai et al., 2005)***. The organism causes invasive infections, such as bacteremia and meningitis, as well as pneumonia and upper respiratory tract infection including otitis media and sinusits ***(Kaplan et al., 1998)***.

The first vaccine to help prevent pneumococcal disease, the seven-valent pneumococcal conjugated vaccine (PCV7), prevnar (Lederle laboratories/Wyeth-Ayerst). Was licensed in US by US FDA on Februry 2000, it includes seven purified capsular polysaccharides of streptococcal pneumonia ***(Prevnar Information, 2012).***

The vaccine contains capsular polysaccharides from serotypes 4, 9v, 14, 19f and 23f and oligosaccharide from 18c, 6B, the carrier protein CRM 197, and aluminum phosphate adjuvant ***(Raymond et al., 2003).***

Prevnar works by exposing the child to a small dose of the bacteria or a protein from the bacteria, which causes the body to develop immunity to the disease. Prevnar will not treat an active infection that has already developed in the body ***(Prevnar Information, 2012).***

AIM OF THE STUDY

The aim of this study is to assess antibody response to a seven valent pneumococcal conjucated vaccine in children with chronic liver disease.

CHRONIC LIVER DISEASES

The liver is among the most complex and important organs in the human body. Its primary function is to control the flow and safety of substances absorbed from the digestive system before distribution of these substances to the systemic circulatory system. A total loss of liver function leads to death within minutes, demonstrating the liver's importance ***(Marieb, 2001)***.

Chronic liver disease is one of the main reasons of admission in the children age group. Although the number of such cases is not high but because of the chronic and often incurable course of most cases, extra care and attention should be paid to their complications, prevention and life quality improvement ***(Behmanesh et al., 2010)***.

Chronicity of liver disease is determined either by duration of liver disease (typically > 6 months) or by evidence of either severe liver disease or physical stigmata of chronic liver disease (clubbing, spider telangiectasia and hepatosplenomegaly) ***(Behmanesh et al., 2010)***.

The severity is variable; the affected child may have only biochemical evidence of liver dysfunction, may have

stigmata of chronic liver disease, or may present in hepatic failure. Chronic liver disease may be caused commonly by persistent viral infections, metabolic diseases, drugs, autoimmune hepatitis, or unknown factors ***(Benjamin & Frederick, 2007)***.

❖ Embryology of liver:

During the third week of gestation the liver bud (hepatic diverticulum) develops as an outgrowth from the endodermal epithelium of the ventral foregut. The bud consists of rapidly developing cell strands which grow through the septum transversum (a mesodermal plate between the pericardial cavity and the yolk sac from which connective tissue, haemopoietic cells and Kupffer cells derive). The strands continue to grow through the septum forming thick plates of hepatocytes whilst the connection with the foregut narrows and becomes the common bile duct ***(Nagaki and Moriwaki, 2008)***.

The blood supply to the liver influences the growth of the liver. The two vitelline veins (which ultimately join to become the portal vein) initially supply the developing liver. Later in embryogenesis initially both umbilical veins provide blood to the liver and then the right disappears leaving the left to perfuse the whole liver. The left umbilical vein supplies the

left lobe sinusoids, mixes with left branch portal blood flow to provide retrograde flow to the right lobe sinusoids (50% of the blood to the right lobe is supplied from the portal vein which is nutrient poor) and also flows into the inferior vena cava via the ductus venosus ***(Hartley, 2010)***.

The arterial supply develops later in embryogenesis and is closely related to the development of the bile ducts. The external biliary system (including the gallbladder) is derived from the hepatic diverticulum. The intrahepatic bile ducts develop independently of the extrahepatic and only towards the end of foetal development do the two structures join. The hepatoblasts which surround the mesenchyme of the portal vein tracts become smaller and form a single cell sheath around the portal vein known as the ductal plate ***(Lamaigre, 2008)***.

❖ Anatomy of liver:

The liver is the largest visceral organ in the body. It lies below and on the right side of the diaphragm. Except for the portion that is in the epigastric area, the liver is contained within the rib cage and in healthy persons cannot normally be palpated. The liver is surrounded by a tough fibro-elastic capsule called *Glisson's capsule* ***(Guyton & Hall, 2000)***.

The liver is unique among the abdominal organs in having a dual blood supply the *hepatic artery* and the *portal vein*. Approximately 300 mL of blood per minute enters the liver through the hepatic artery; another 1050 mL/minute enters by way of the valveless portal vein, which carries blood from the stomach, the small and the large intestines, the pancreas, and the spleen1. Although the blood from the portal vein is incompletely saturated with oxygen, it supplies approximately 60% to 70% of the oxygen needs of the liver ***(Klammt et al., 2007)***.

The *lobules* are the functional units of the liver. Each lobule is a cylindrical structure that measures approximately 0.8 to mm in diameter and several millimeters long. There are approximately 50,000 to 100,000 lobules in the liver. Each lobule is organized around a central vein that empties into the hepatic veins and from there into the vena cava. The terminal bile ducts and small branches of the portal vein and hepatic artery are located at the periphery of the lobule. Plates of hepatic cells radiate centrifugally from the central vein like spokes on a wheel (fig.1). These hepatic plates are separated by wide, thin-walled channels, called *sinusoids*, which extend from the periphery of the lobule to its central vein ***(Guyton & Hall, 2000).***

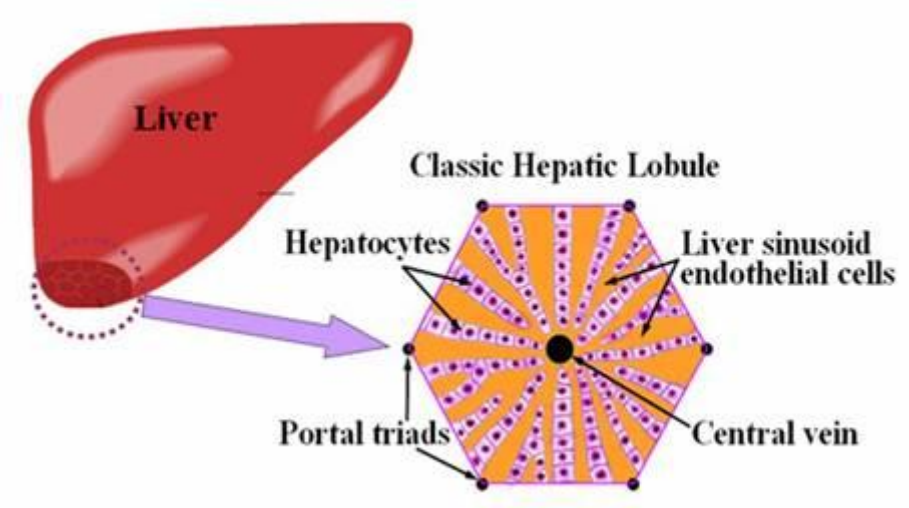

Figure (1): Hepatic lobule ***(Guyton & Hall, 2000).***

❖ Function of the liver

Existing at the crossroads between the digestive tract and the other functions of the body, the liver is charged with the enormous task of maintaining metabolic homeostasis. This involves processing normal dietary elements, such as lipids and carbohydrates, as well as detoxifying and excreting waste products and pollutants. Consequently, hepatic malfunction can have dramatic repercussions ***(Klammt et al., 2007)***.

The liver is a complex organ with many diverse functions. Unlike many other organs in the body the liver has the capacity to self repair and regenerate.physiology of the liver can be arbitrarily divided into:-

- Formation and excretion of bile
- Synthesis of clotting factors and proteins
- Immune function – formation of immune products and defence
- Excretion of hormones, drugs and waste products
- Storage of vitamins, minerals and nutrients
- The processing of nutrients from digestion.

(Russell, 2003)

Bile acid physiology

Bile salts are formed by and circulated through hepatocytes. They are excreted into bile canaliculi where they mix with water and ions to form bile. The bile canaliculi join in ever increasing sizes to form bile ducts. Bile is stored in the gallbladder which in the presence of cholecystokinin (secreted due to a fat contain meal) empties bile into the small intestine to aid digestion and absorption of dietary fats including fat soluble vitamins. Bile salts are then recycled through the intestine back to the liver ***(Russell, 2003)***.

Hepatic synthesis of albumin

Albumin synthesis begins in the nucleus, where genes are transcribed into messenger ribonucleic acid (mRNA). The mRNA is secreted into the cytoplasm, where it is bound to

ribosomes, forming polysomes that synthesize preproalbumin. Preproalbumin is an albumin molecule with a 24 amino acid extension at the N terminus. The amino acid extension signals insertion of preproalbumin into the membrane of the endoplasmic reticulum ***(Klammt et al., 2007)***.

Once inside the lumen of the endoplasmic reticulum, the leading 18 amino acids of this extension are cleaved, leaving proalbumin (albumin with the remaining extension of 6 amino acids). Proalbumin is the principal intracellular form of albumin. Proalbumin is exported to the Golgi apparatus, where the extension of 6 amino acids is removed prior to secretion of albumin by the hepatocyte ***(Hartley, 2010)***.

Once synthesized, albumin is secreted immediately; it is not stored in the liver. Albumin transports various substances, including bilirubin, fatty acids, metals, ions, hormones, and exogenous drugs. One consequence of hypoalbuminemia is that drugs that are usually protein bound are free in the plasma, allowing for higher drug levels, more rapid hepatic metabolism, or both ***(Klammt et al., 2007)***.

Hepatic excretion of hormones and drugs

The conjugation process in the liver also plays a major role in excreting cholesterol, hormones, and drugs from the body ***(Hartley, 2010)***.

Hepatic processing and storage of vitamins, minerals and nutrients

The liver plays an important role in metabolizing nutrients such as carbohydrates, proteins, and fats. The liver helps metabolise carbohydrates in three ways:

- Through the process of glycogenesis, glucose, fructose, and galactose are converted to glycogen and stored in the liver.
- Through the process of glycogenolysis, the liver breaks down stored glycogen to maintain blood glucose levels when there is a decrease in carbohydrate intake.
- Through the process of gluconeogenesis, the liver synthesizes glucose from proteins or fats to maintain blood glucose levels.

(Hartley, 2010)

Liver cells also chemically convert amino acids to produce ketoacids and ammonia, from which urea is formed and excreted in the urine. Digested fat is converted in the

intestine to triglycerides, cholesterol, phospholipids, and lipoproteins. These substances are converted in the liver into glycerol and fatty acids, through a process known as ketogenesis ***(Hartley, 2010)***.

Formation of Coagulation factors:

The liver plays a central role in the hemostatic system because it produces the majority of the coagulation factors, anticoagulation factors, and fibrinolytic proteins found in plasma ***(Tripodi & Mannucci, 2011)***.

❖ Epidemiology of chronic liver disease:

HBV is the most common cause of cirrhosis and hepatocellular carcinoma in the world today. Of approximately 2 billion people who have been infected with HBV worldwide, more than 350 million, or about 5% of the world's population are chronic carriers, and with an annual incidence of more than 50 million (WHO, 2000). HBV accounts for 500,000 to 1.2 million deaths per year ***(Lavanchy, 2004)***.

Egypt holds a unique position in the epidemiology of hepatitis and liver cancer. It has successfully implemented the hepatitis B virus (HBV) vaccine and now boasts 95%- 100% coverage ***(Mangoud et al., 2004)***.

More than 3 % of the world population or about 170-5 million people may be infected with HCV ***(Dienstag & McHutchison, 2006).*** The prevalence of HCV is increasing and estimates of the future burden of chronic hepatitis C predict at least a 3 fold rise in chronic liver disease and cirrhosis by the year 2020 ***(Law et al., 2003).***

Egypt is also home to the highest prevalence of hepatitis C virus (HCV) in the world, with an overall rate of approximately 22% ***(Deuffic-Burban et al., 2006)***.

The prevalence rate of HCV in children is much lower than adults, ranging between 2-10%. While the rate in children is much lower than that in the older population, it is still considered high by World Health Organization (WHO) standards, where rates greater than about 4% are considered high (fig.2) ***(Arafa et al., 2005)***. Therefore, as more and more countries adopt the HBV vaccine, HCV could become the dominant force driving liver cancer rates worldwide ***(Raptis et al., 2003)***.

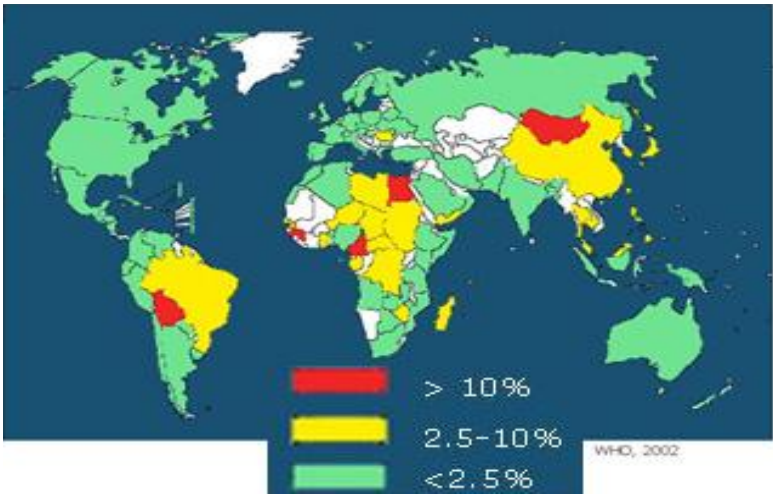

Figure (2): Global Prevalence of Chronic HCV Infection in 2001 ***(Arafa et al., 2005)***.

Nonalcoholic fatty liver disease (NAFLD) affects 10-30% of the general population in various countries. 10% of these people, or about 2-3% of the general population, satisfy the criteria for nonalcoholic steatohepatitis, (NASH). The prevalence of NAFLD is also expected to rise in developed countries given the epidemic of its major determinant, obesity ***(Clark, 2006).***

Studies indicate that advanced fibrosis and cirrhosis will develop in 20-40% of patients with chronic hepatitis B or C and in a similar proportion of patients with nonalcoholic fatty liver disease ***(Memon & Memon, 2002; Lavanchy, 2004; Dienstag & McHutchison, 2006)***.

❖ Pathogenesis of CLD:

Chronic infections with hepatitis B and C viruses, and non-alcoholic fatty liver diseases are important causes of CLD. The major determinant in their prognosis is the progressive accumulation of fibrosis, with distortion of the hepatic architecture, and ultimate progression to cirrhosis and its allied complications ***(Dienstag & McHutchison, 2006)***.

In the recent years, with the great advancement in therapeutic modalities to treat chronic liver diseases, accurate assessment of fibrosis has become of paramount importance; to guide management decisions, predict outcome (prognosis), and monitor disease activity in individual patients ***(Parkes et al., 2006)***.

Fibrogenesis is a ubiquitous process in chronic inflammatory diseases in human beings, in response to injury. Progressive fibrosis with the development of cirrhosis, is a complication of all chronic liver diseases whatever their etiology, whether viral, autoimmune, biliary, toxic, or metabolic disease ***(Friedman, 2003)***.

Fibrogenesis is a non-specific mechanism, which lasts as long as injury persists and is believed to help limit the extension of inflammatory reaction. Fibrosis, therefore, is a