REVIEW PAPER

Chronic Liver Disease in Patients with Schizophrenia: A Review

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Abstract

Introduction: Schizophrenia is a chronic psychotic disorder characterised by severely impaired behaviors, thinking, and emotion. Patients with schizophrenia are closely related to chronic liver disease. The prevalence of chronic liver disease in patients with schizophrenia (7.0%) was 1.27 times as high as that of the general population (6.1%). This is due to many reasons such as metabolic syndrome, effects of antipsychotic drugs, alcohol consumption and smoking. Objectives: The objectives of this review paper are to discuss about the common terms related to chronic liver disease and the relationship between chronic liver disease and schizophrenia. Discussion: Chronic liver disease is divided into few types like non-alcoholic fatty liver disease, hepatitis, cirrhosis and many more. The types depend on the aetiology of the disease. There are specific mechanisms on how the schizophrenia and chronic liver disease are related to each other. Conclusion: In conclusion, metabolic syndrome, the usage of antipsychotics drug, alcohol consumption and smoking are the main factors that can lead to chronic liver disease in schizophrenia patients. It is important to make all people related with this disorder to understand the mechanism, which may help schizophrenia patients to prevent from the liver disease.

Keywords: Schizophrenia, Chronic Liver Disease, Metabolic Syndrome, Patients

Introduction

World Health Organization (2014) defines schizophrenia as a "severe mental disorder, characterized by profound disruptions in thinking, affecting language, perception, and the sense of self. It often includes psychotic experiences, such as hearing voices or delusions. It can impair functioning through the loss of an acquired capability to earn a livelihood, or the disruption of studies". Besides, it can affect more than 21 million people globally, due to the nature of it as a treatable disorder [1]. Schizophrenia is a serious disorder of the brain and mind but with the potential to be treated [2].

The probability of men to get schizophrenia slightly earlier than women, whereas the rate ratio for men : women was 1.4:1 [3]. The median lifetime morbid risk for schizophrenia was 7.2/1,000 persons [4].

Most women develop symptoms several years later than men, and the incidence in women is prominently higher in women after the age of 30. The average age of onset this disease for men is 18 while for women is 25. For young patients below 10 years old and elderly people over the age of 40 years old, schizophrenia onset is quite rare. In average, most people were diagnosed as schizophrenia when they reached 18 years old, with the prevalence rate of 1.1%[5].
Based on the research done by people with schizophrenia, they have high mortality rate with a 2 to 3 fold increased risk of dying (median standardized mortality ratio of 2.6 for all-cause mortality), and this differential gap in mortality has raised over several decades. Moreover, the highest overall mortality was observed among patients with no antipsychotic exposure [4, 6].

The main reasons of this high mortality rate are cancer, suicide, and cardiovascular disease, with evidence that cancer mortality rates are as similar as cardiovascular mortality rates. The factors contribute to mortality are based on cohort ages, follow up length and study type. Antipsychotic treatments reduce mortality in comparison to no treatment at all, and atypical antipsychotics do not seem to rise up the cardiovascular mortality and morbidity compared with the typical antipsychotics [7].

The typical antipsychotic drugs are also knonw as the “conventional” antipsychotic drugs which have high affinity antagonists towards dopamine D2 receptor that are in turns, give the most effective against psychotic symptoms but with high rates of neurologic side effects that are unwanted such as extrapyramidal symptoms [8]. These older medications are also not so effective against schizophrenia negative symptoms such as lack of emotional expressiveness, apathy, and decreased motivation [9].

In 1989, atypical antipsychotics, which also known as the second generation antipsychotics were introduced [10]. At the correct dosages, less neurological side effects were produced, which include painful spasms, muscular rigidity, tremors, or restlessness [8]. This is due to the difference in pharmacological aspects in which the atypical drugs have lower affinity to D2 receptors but have high affinity towards the other neuroreceptors including those for serotonin and norepinephrine [11].

The first of the second-generation antipsychotics, Clozapine, has been shown to be effective among other antipsychotics which had been failed. This is because, clozapine is not connected with the side effects mentioned previously. However, it does produce other side effects, including the possibility of reducing the number of infection-fighting white blood cells, weight gain, and changes in blood sugar and cholesterol. The serious side effects of Clozapine appear to expose patients towards the death risk from cardiovascular disease due to clozapine associated medical conditions such as obesity, diabetes, hyperlipidemia, and hypertension. [12].

Other atypical antipsychotics include Quetiapine, Risperidone, Aripiprazole, Ziprasidone, Lurasidone. Another atypical antipsychotic which is known as Iloperidone, has been FDA-approved for acute schizophrenia treatment. The utilization of all these medications has resulted with successful cases of schizophrenia patients who can be released back to their community and homes. Clinical judgement and careful monitoring of all the patients who are currently prescribed with the atypical antipsychotic

drugs are necessary, due to the lack of definitive scientific data on the differential effects of antipsychotic drugs in inducing diabetes. Nevertheless, ziprasidone and aripiprazole have not been shown to produce weight gain or diabetes, but more diabetogenic effects information on the of these drugs are needed [13].

Cardiovascular diseases are the major disease associated with schizophrenia [14]. Schizophrenia patients generally need long-term antipsychotic treatment and in the same time, have poor diet variety with an unhealthy lifestyle. These patients are at elevated risk of gaining more weight, contributing to obesity and metabolic syndrome [15, 16]. Moreover, higher liver disease prevalence in schizophrenia patients had been found, if compared to normal population [17].

Objectives

The objectives of the current review are to discuss about the common terms related to chronic liver disease and the relationship between chronic liver disease and schizophrenia. Furthermore, the discussion will continue with the mechanism on how the mental illness can lead to chronic liver disease.

Discussion

Chronic Liver Disease

Chronic liver disease is the marked by the slow and continuous destruction of liver tissue over time. Urgent medical care is required for this life-threatening condition. Chronic liver diseases include alcoholic fatty liver, alcoholic liver cirrhosis, alcoholic liver damage, acute alcoholic hepatitis, liver cirrhosi without mention of alcohol, unspecified chronic hepatitis, other chronic non- alcoholic liver disease, biliary cirrhosis, and unspecified chronic liver disease without mention of alcohol. The common causes of chronic liver disease are Hepatitis C and B, cirrhosis, long term alcohol consumptions, malnutrition, as well as hemochromatosis which is an inherited disorder that contributes to absorption and storage of too much iron in the body [18].

Early symptoms of liver disease include loss of appetite, fatigue, diarrhea, and nausea. However, as the condition is reaching the development of liver failure, the symptoms become more serious, and need urgent care. Among the related symptoms are jaundice, bleeding easily, swollen abdomen, mental confusion or disorientation which is known as hepatic encephalopathy, sleepiness and even coma. Jaundice has been known as the most important symptoms that indicate the damage of the liver. Jaundice is the yellowish color of skin and mucous membranes due to bile pigments accumulation in blood and eventually depositied in body tissues. Jaundice should be differentiated from cholestasis, which refers to a decreased rate of bile flow. Asparatate amino-transferase and alanine aminotransferase were significantly higher in jaundiced patients [19].

Chronic liver disease and Schizophrenia are close related to each other. This is because patients with Schizophrenia have high prevalence to chronic liver disease. In 2000, the chronic liver disease prevalence in schizophrenia patients was 7.0%, which was 1.27 times higher than that of the general population which was only 6.1% [20]. From 2001 to 2010, the average annual incidence of chronic liver disease in schizophrenia patients was also higher than the general population (2.9% vs 2.5%, risk ratio of 1.15; 95% confidence interval, 1.07–1.24). The mechanism on how schizophrenia can lead

to chronic liver disease will be discussed further, at the end part of this review.

Metabolic syndrome

Schizophrenia patients have high metabolic syndrome prevalence that may contribute to an increased risk of Non-Alcoholic Fatty Liver Disease (NAFLD) [20]. Based on the research done by Liao C.H. [21], the metabolic syndrome prevalence among schizophrenia patients may range from 24% to 43% in men and 27%–52% in women. NAFLD, which is the liver manifestation of the metabolic syndrome, is now known as the most commonly occurring global liver problem. This apparent 'epidemic', coupled with several evidences that show a significant amount of NAFLD patients can develop to cirrhosis, hepatocellular carcinoma (HCC), and liver failure [22].

Identification of metabolic syndrome is related to the presence of at least 3 of the following components: abdominal obesity (waist circumference of more than 88 cm for females and more than 102 cm for males,), increased triglycerides (for more than 150 mg/dl or on drug treatment for elevated triglycerides), decreased HDL-C level (for less than 50 mg/ dl in females and less than 40 mg/dl in males, or on drug treatment for reduced HDL-C), hypertension (systolic blood pressure of more than130 mmHg or diastolic blood pressure of less than 85 mm Hg or on antihypertensive drug treatment) and impaired fasting blood glucose (100 to 125 mg/dl or on antidiabetic drug treatment) [23].

Hypertension

Hypertension that is related to schizophrenia has been associated with higher body weight and metabolic syndrome due to the patients' own sedentary life style [24-26]. Portal hypertension can contribute to chronic liver disease. Portal hypertension occurs mainly from augmented resistance to blood flow in the portal vein. A common reason of this resistance is disease within the liver; uncommon reasons include blockage of the portal or splenic vein and impaired hepatic venous outflow. Increased volume flow is a rare reason, although it often leads to portal hypertension in cirrhosis and in hematologic disorders that contributes to the massive splenomegaly [27].

Diabetes

There are several aspects associated with the high incidence of diabetes among schizophrenia patients include genetic factors, lifestyle, obesity, and medication effects [28]. The association of schizophrenia is stronger for diabetes mellitus than for hyperlipidemia and hypertension. Antipsychotics are associated with the increased risk for metabolic abnormalities [21]. Moreover, female schizophrenia patients show a much higher prevalence if compared to the females of the general population. A French cohort study reported that female schizophrenia patients were twice more likely to be diagnosed with diabetes, if compared to the women in general population [29].

Antipsychotic drugs use may lead to diabetes due to the possibilities of glucose metabolism interruption [30]. Nevertheless, drug-induced body weight gain may be detected because of an increase in appetite, due to the receptor blockade [31]. Moreover, schizophrenia patients may have an unhealthy lifestyle (a diet lower in fiber and higher in fat with very little exercise and heavy smoking), which may contribute to health problems such as diabetes, obesity, excess mortality and hypertension [32].

A clinical professor of medicine at the University of California, San Diego, who is known as Dr Daniel Einhorn, stated that "people with diabetes also have obesity and insulin resistance, and so the fatty liver is thought to be part of that" [33]. China has shown consistent increase of fatty liver prevalent over the recent years, accompanying in people's living conditions improvements and a more westernized diet adoption [33].

The liver plays a significant role in the regulation of glucose in human body. Initially, transportation of glucose starts from the intestines to the liver, which is converted to glycogen for storage or directly used for fuel. The usage of glucose as fuel is facilitated by insulin receptors in liver, muscle, and fat cells. Insulin helps glycogen storage and regulates the entry of glucose into tissues. Metabolism of insulin occurs in the liver, where it promotes the production of protein, cholesterol, glycogen, and triglycerides and excites the formation of low density lipoproteins (LDL) which involve in the transportation of cholesterol into the arteries [34].

In diabetes, high fasting blood sugars is contributed by the excessive output of glucose by the liver. Failure of insulin to suppress hepatic glucose production (HGP) has been found to be the key defect in type 2 diabetes mellitus. The inhibition of HGP by insulin is either through direct or indirect means, the latter of which include the glucagon secretion inhibition, decrease in the amount of gluconeogenic substrates load, which is when reaching the liver, will change in neural signaling to the liver, and reduction in plasma nonesterified fatty acid level [35].

The nonalcoholic fatty liver disease risk is increased in diabetes [36]. Commonly, in diabetics, extra glycogen may be linked to the liver fat accumulation. When transportation of fat from the intestines to the liver is increased and removal from the liver is decreased, fat deposits will be developed. This condition may due to obesity and diabetes, but the exact reasons are still unknown [37].

Hyperlipidemia

The schizophrenia patients may have a higher risk of developing hyperlipidemia associated with schizophrenia. This is because, schizophrenia patients may prone to obesity due to unnatural lifestyle with condensed physical activity and poor diet selection. [38-40]. In a Taiwan study, among the adolescents, the prevalence of NAFLD was 39.8%, but for overweight and obese subjects, their chance is increased, due to the progressive increase of the incidence to 50.5% and 63.5% [41]. However, the findings may be underestimated due to the non-standardization of recognition and management of cholesterol in schizophrenic patients [42].

Hyperlipidemia with a marked increase of low-density lipoprotein (LDL) and less amount of high-density lipoprotein (HDL) [43]. Hyperlipidemia can cause obesity which can lead to chronic liver disease [44]. It is estimated that 75% of obese individuals are at risk of developing a simple fatty liver. Moreover, obese individuals are at 23% of more risk of developing fatty liver with inflammation [45].

The key factor for the inflammation development includes the extra supply of free fatty acids (FFA) to the liver, due to obesity and the associated insulin resistance in adipose tissue. This extrahepatic insulin resistance may arise, because of macrophages infiltration of adipose tissue in

obesity, releasing cytokines capable of impairing insulin signaling (Interleukin (IL)-6, IL-1β, and TNFα,). Once taken up by the liver, as well as being stored as triglyceride and oxidised, FFA activate the transcription factor NF-κB which functions as the 'master regulator' of pro-inflammatory cytokine, chemokine and adhesion molecule gene transcription [46].

Subsequently, classical inflammatory cells including Kupffer cells are activated due to the release of cytokines from hepatocytes, including TNFα [47]. Then, more cytokines are produced, starting hepatocyte injury by apoptosis/necrosis in conjunction with oxidative stress arising due to the high FFA oxidation. In addition, these cytokines also are contributing to hepatic insulin resistance, leading to increased hepatic FFA oxidation and possibly will lead to extrahepatic insulin resistance in adipose and muscle tissues [47].

Antipsychotic drugs

The schizophrenia patients may receive either typical antipsychotic or atypical antipsychotic treatment. There possibilities of developing hepatic injuries from this treatment. The events may occur as early as in the first week of treatment or be delayed its onset anywhere from several weeks to months [48]. Asymptomatic increases in liver enzymes or even serious liver injury are commonly associated with the prescription of atypical antipsychotics for schizophrenia patients [49].

Nevertheless, the use of typical antipsychotics and atypical antipsychotics could lead to chronic liver diseases, such as NAFLD, by causing a worsening metabolic profile in schizophrenia patients[20]. The ranking of the medications that induced liver injury are antimicrobials (antiviral agents, antibacterial agents, antituberculosis agents, and others) in 45.5%, central nervous system agents (antipsychotics, antidepressants, and antiepileptic agents) in 15%, immunomodulatory agents in 5.5%, analgesics (muscle relaxants and nonsteroidal agents) in 5%, antineoplastic agents in 4%, lipid-lowering agents in 3.4%, and antihypertensive agents in 5% [50].

The example of antipsychotic induced liver disease may be referred to phenothiazines, which are well established causes of a cholestatic injury arising within 1 to 4 weeks of initiating treatment. Indeed, chlorpromazine was one of the most common causes of drug induced liver disease ("Thorazine jaundice") during the 1960s and early 1970s,. The other phenothiazines were found to cause a similar cholestatic hepatitis, although much less frequently than chlorpromazine [51].

A study done by Atasoy et al. [52], found that two out of the 110 patients (1.8%) presented with 4 fold of elevated AST levels and 3 fold of elevated ALT levels and required to halt treatment (elevated AST in one woman with olanzapine dose of 20 mg per day; elevated ALT in one man with olanzapine dose of 30 mg per day). Thirty out of the 110 patients (27.2%) showed asymptomatic elevated levels of AST, ALT, GGT, and serum bilirubin levels in the first month of the study. Then, after 6 months of the treatment, 25 patients (22.7%) experienced abnormalities in the liver function tests.

Alcohol Consumption

There is a significance prevalence of hazardous alcohol use in schizophrenia patients [53]. Alcohol can cause inflammation in the liver, which occurs long term. Over time, scarring and even cirrhosis

can take place. Cirrhosis is considered as the final phase of alcoholic liver disease [54]. The most prevalent types of alcoholic liver disease are alcoholic hepatitis, fatty liver, and cirrhosis. Commonly, as people continue to drink alcohol heavily, they progress from fatty liver, develop to hepatitis, and eventually become cirrhosis [55].

According to the Dietary Guidelines for Americans, moderate drinking of alcohol is up to 2 drinks per day for men and up to 1 drink per day for women. High consumption of alcohol has been associated with elevated risk of chronic liver disease. This is because nearly 20% of alcoholics and heavy drinkers develop steatosis or fatty liver. Majority of the cases, clinical symptoms are hard to seen except for a hepatomegaly (an enlarged liver). The condition of fatty liver can be managed by either stopping or reducing alcohol consumption, but it can lead to death if no effort of stopping or reducing the alcohol consumption [55].

Alcohol consumption may contribute to alcoholic hepatitis. The hepatitis is known as inflammation which can be ranged from mild to severe. Mild hepatitis may not produce any symptoms. However, the only way inflammation can be identified is by observing the abnormal level of liver enzymes in the blood, which can be done by a blood test. If heavy drinking still remains, nearly 40% of alcoholic hepatitis cases will progress into alcoholic cirrhosis [55].

Besides, the last stage of liver disease is cirrhosis. Roughly, 10 to 15% of alcoholism people experienced cirrhosis [55]. When the scar tissue (fibrosis) is replacing the normal liver tissue, cirrhosis is said to occur. The scar tissue changes the normal structure of liver and interrupt the regrowth process of liver cells. As scar tissue develops gradually, liver cells become damaged and died. Nevertheless, blood flow through the liver may also be affected by the scar tissue. Eventually, this condition may cause back pressure in the blood vessels, which in turn, bring back blood to the liver [56].

Smoking

Patients with schizophrenia have high prevalence to chronic liver disease due to unhealthy lives of the patients like smoking [20]. There are several definitions of heavy smokers. Some studies stated exposure to more than one packets ($\geq$ 40 cigarettes) a day for more than 10 years. Alternatively, Marrero et al. [57], have stated exposure to greater than 21 and above pack-years. Liver function can be affected by cigarette smoke indirectly by the oxidative stress increment of the system that will reach the liver, contributing to the irreversible damage of the liver cells. Nevertheless, association of tobacco smoking and liver cancer risk had been consistently reported in cohort and case control studies [58].

There are some population-based studies that confirmed a low-grade systemic inflammatory response is evident in smokers. Among the signs are elevated levels of fibrinogen, interleukin-6, C-reactive protein (CRP), as well as WBC counts. Moreover, coagulation, blood and/or plasma viscosity, rheologic, and endothelial function markers like fibrin d-dimer, hematocrit, tissue plasminogen activator antigen, circulating adhesion molecules (intracellular adhesion molecule-1, selectins), and plasminogen activator inhibitor type I are changed in chronic cigarette smokers [59].

Chemical compounds are mixed in a cigarette smoke. They can either be bound to aerosol particles or freely floating in the gas

phase. They can undergo some reactions to form other constituents and can be distilled into smoke. It has been estimated that there are 7,357 chemical compounds from many different classes exist in cigarette smoke. These chemicals in cigarette smoke will eventually make their way to the liver [60].

Liver cells damage and fibrosis will be resulted from the oxidative stress on the liver caused by the chemicals of cigarette smoke. Basically, body organs undergo aging process, and oxidative stress is involved. Free radicals that make body cells damage are produced by oxidation process. This process contributes to a major part in the chronic and degenerative illness development such as rheumatoid arthritis, cataract, autoimmune disorders, cancer, aging, cardiovascular and neurodegenerative diseases [61].

Chemical substances produced from smoking has a cytotoxic potential which increase necroinflammation and fibrosis. Additionally, the production liver cell injury is associated with pro-inflammatory cytokines such as IL-1, IL-6 as well as TNF-α that are increased from smoking as well. It contributes to the secondary polycythemia development and eventually makes red cell mass increment and turnover which might be a reason to the secondary iron overload disease leading to hepatocytes oxidative stress [62].

Conclusion

In conclusion, metabolic syndrome, the usage of antipsychotics drug, alcohol consumption and smoking are the main factors that can lead to chronic liver disease in schizophrenia patients. The specific mechanisms related to each of the factors should be known to avoid the serious complication. It is important to practice healthier lifestyles modification, which may help schizophrenia patients to prevent from the liver disease.

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