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Original Article

Administration of Selective Serotonin Reuptake Inhibitors and Risk of Pyogenic Liver Abscess in a Case-Control Study

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1. Abstract

1.1. Background/Objective: Little research is available between Selective Serotonin Reuptake Inhibitors (SSRIs) use and incidence of Pyogenic Liver Abscess (PLA). The objective of the study was to determine whether SSRIs use is associated with PLA.

1.2. Methods: There were 1749 subjects, who had the first episode of PLA between 2000 and 2013, were considered as the cases and 6518 subjects without PLA as the matched controls. SSRIs use was defined as 'current', 'recent' or 'past' if the prescription was filled < 3 months, 3–6 months or ≥ 6 months before the index date, respectively. The Odds Ratio (OR) and 95% Confidence Interval (CI) of PLA associated with SSRIs use was measured by the multivariable logistic regression model.

1.3. Results: The adjusted ORs of PLA was 1.26 for subjects with current use of SSRIs, 1.04 for subjects with recent use, and 0.8 for subjects with past use, compared with never users. In further analysis, the adjusted OR of PLA was 1.01 for subjects with increasing cumulative duration of SSRIs use for each additional month of use, compared with never users.

1.4. Conclusion: No significant association, including duration-dependent effect can be detected between SSRIs use and the risk of PLA.

2. Keywords: liver; clinical pharmacology; epidemiology; outcome research

3. Introduction

The pathophysiology and prognosis of Pyogenic Liver Abscess (PLA) was first described and quoted by Hippocrates, the God of Science and Medicine in 19th century [1]. After a long period of time, Ochsner and Debakey defined the etiology, mortality and treatment of PLA [2]. At that time, surgical treatment was the first choice for patients with PLA until the mid-1980s [3]. In the late 20th century, Percutaneous Drainage (PCD) and Percutaneous Needle Aspiration (PNA) under ultrasonic guidance became the preferred and safer method to treat patients with PLA, replacing traditional surgery [4, 5].

PLA, although uncommon, affect the consumption of healthcare resources, due to significant increase in associated morbidity and mortality in North America [6], Canada [7] and Denmark [8]. At the same time, PLA is a life-threatening disease, caused by the well-known and common pathogen Escherichia Coli worldwide [9]. Recently, some small studies in Taiwan and South Korea revealed that Klebsialla pneumoniae is the primary pathogen for PLA [10, 11]. The discrepancy might be due to racial and geographic characteristics. Furthermore, the risk factors associated with mortality from PLA include age, bacteremia, cirrhosis, renal failure and malignancy [12, 13], and the mechanism still remains largely unclear.

In addition, the etiology, definition and pathogenesis of PLA along with its epidemiology is still blurry and dramatic due to its fluctuation of incidence in recent decades. Previously, the incidence of PLA reported was scarce, ranging from 1.1to 2.3 per 100000 population [7, 8, 12] in Denmark and Canada, respectively. But about 13 years ago, one retrospective study showed higher incidence rate of 17.6 per 100000 populations in Taiwan [13].

Serotonin (5-hydroxytryptamine, 5-HT), is a monoamine neurotransmitter, which is biochemically derived from amino acid tryptophan, mainly detected in the gastrointestinal tract and central nervous system in human beings [14]. It is also well known for contributing to the etiology of happiness and well-being feeling experienced by human beings [15]. Hence, drugs which can alter serotonin levels in plasma are used for treating Major Depressive Disease (MDD). Serotonin is metabolized by monoamine oxidase to the corresponding aldehyde, which is mainly carried on in the liver. Monoamine oxidase inhibitors prevent the catabolism of most neurotransmitters, including serotonin, thereby, increasing the plasma levels in the brain [16]. Owing to the former mechanism, SSRIs were used for treating major depressive and anxiety disorders.

Drug-Induced Liver Injury (DILI), the fourth leading cause of liver damage in the western countries, is an important issue related to physician's prescription medicines because it causes irreversible damage of liver and is easily neglected [17]. Otherwise, the damage resulted from antidepressants, including SSRIs, usually is asymptomatic and rare [18]. Some clinical manifestations of DILI e.g., fever, fatigue and abnormal liver functions or elevation of White Blood Count (WBC), are similar to PLA. Owing to the reasons mentioned above

(i) Few studies exist that explore the relationship between SSRIs and PLA in Taiwan and also worldwide,

(ii) SSRIs are commonly used globally and any potential risk of increasing disease incidence due to its side effects, have important clinical implications.

(iii) several clinical manifestations of PLA and DILI from SSRIs are similar.

We used large scale NHI data to investigate the relationship between SSRIs use and PLA.

4. Methods

4.1. Design and Data Source

Taiwan is an independent country with more than 23 million residents [19-21]. This was a population-based case-control study using the database of the Taiwan National Health Insurance Program. The program was launched in March 1995, with coverage rate of more than 99.6% of the population of Taiwan [22]. This study was approved by the Ethics Review Board of China Medical University and Hospital in Taiwan (CMUH104-REC2-115). The details of the program have been well documented in previous studies [23-25].

4.2. Study Subjects

We selected subjects aged 20 to 84 years with the first-episode of pyogenic liver abscess during the period between year 2000 and 2013 as the cases (based on International Classification of Disease, 9th Revision of Clinical Modification, ICD-9 code 572.0). The diagnosis date of pyogenic liver abscess was defined as the index date. Subjects aged 20 to 84 years without a diagnosis of pyogenic liver abscess were selected from the same database as the matched controls. The cases and the controls were matched for sex, age (every 5-year span), comorbidities, and index year of diagnosing pyogenic liver abscess. To reduce biased results, subjects with prior diagnosis of amebic liver abscess (ICD-9 code 006.3), or liver transplantation (ICD-9 codes 996.82 and V42.7) before the index date were excluded from the study.

4.3. Definition of Selective Serotonin Reuptake Inhibitors Use, and Non-Selective Serotonin Reuptake Inhibitor Antidepressants Use

To determine the relationship between SSRI's use and PLA, the prescription history of SSRIs before index date was collected. SSRIs available in Taiwan during the year 2000–2013 include: fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, and escitalopram. In Taiwan, the continuous prescription for chronic diseases is refilled every 3 months. Therefore, SSRIs use was categorized by the prescription filled < 3 months, between 3 and 6 months, and ≥ 6 months before index date [current use (< 3 months), recent use (3–6 months), and past use (≥ 6 months)], which was adapted from previous studies [26, 27]. Ever use of non-SSRI antidepressants was defined as subjects who had at least a prescription of non-SSRI antidepressants before index date. Subjects who never had a prescription of medications studied were defined as never use.

4.4. Study Comorbidities

Comorbidities potentially related to pyogenic liver abscess before the index date were: alcohol-related diseases, biliary calculi, chronic kidney disease, diabetes mellitus, as well as chronic liver disease including cirrhosis, hepatitis B, hepatitis C, and other chronic hepatitis. All comorbidities were diagnosed based on ICD-9 codes, which have been well validated in previous studies [14, 28-38].

4.5. Statistical Analysis

We compared the differences of the demographic status, SSRIs, non-SSRI antidepressants use, and comorbidities between the cases and the matched controls by using the Chi-square test for categorized variables and the t-test for continuous variables. At first, all variables were tested by the univariate logistic regression model. Only those variables found statistically significant in the univariate logistic regression model were further included in the multivariate logistic regression model to measure the adjusted Odds Ratio (OR) and 95% confidence interval (95% CI) of pyogenic liver abscess association with SSRIs use. We further conducted an analysis on the risk of pyo-

genic liver abscess associated with cumulative duration of SSRIs use. Analyses were performed by using the SAS 9.2 version (SAS Institute Inc., Carey, North Carolina, USA), with $P < 0.05$ as statistically significant.

5. Results

5.1. Basic Characteristics of the Study Population

Table 1 shows the distributions of sex, age, SSRIs use, non-SSRI antidepressants use, and comorbidities between the cases and the matched controls. The study included 1749 cases with pyogenic liver abscess and 6518 matched controls, with similar distributions of sex and age. The mean ages (standard deviation) of the study subjects were 60.0 years (14.2) in the cases and 59.8 years (14.1) in the matched controls, without statistical significance (t-test, $P = 0.75$). The cases had a higher proportion of current use of SSRIs than the matched controls, without statistical significance (0.6% vs. 0.5%, $P = 0.34$). The cases had statistically higher proportions of alcohol-related disease, biliary stone, and chronic kidney disease than the matched controls ($P < 0.05$).

Table 1: Characteristics between cases with pyogenic liver abscess and matched controls

	Matched controls N= 6518		Cases N= 1749		
Variable	n	(%)	n	(%)	*P* value*
Sex					0.94
Female	2391	(36.7)	640	(36.6)	
Male	4127	(63.3)	1109	(63.4)	
Age group (year)					0.92
20-39	1529	(23.4)	414	(23.6)	
40-64	2449	(37.6)	648	(37.1)	
65-84	2540	(39.0)	687	(39.3)	
Age (years), mean± standard deviation†	59.8±14.1		60.0±14.2		0.75
Selective serotonin reuptake inhibitors					0.34
Never use	6022	(92.4)	1632	(93.3)	
Current use	31	(0.5)	11	(0.6)	
Recent use	24	(0.4)	7	(0.4)	
Past use	441	(6.7)	99	(5.7)	
Ever use of non-selective serotonin reuptake inhibitor antidepressants	496	(7.61)	117	(6.69)	0.19
Comorbidities before index date					
Alcohol-related disease	372	(5,71)	131	(7.49)	0.01
Biliary stone	732	(11.2)	264	(15.1)	<0.001
Chronic kidney disease	580	(8.90)	186	(10.6)	0.03
Chronic liver disease	1852	(28.4)	534	(30.5)	0.08
Diabetes mellitus	2057	(31.6)	587	(33.6)	0.11

Data are presented as the number of subjects in each group with percentages given in parentheses.

*Chi-square test and †*t*-test comparing cases and matched controls

5.2. Risk of Pyogenic Liver Abscess Associated with Selective Serotonin Reuptake Inhibitors Use

Variables found to be statistically significant in the univariate model were further included in the multivariate logistic regression model (Table 2). After adjusted for alcohol-related disease, biliary stone, and chronic kidney disease, the adjusted ORs of pyogenic liver abscess were 1.26 for subjects with current use of SSRIs (95% CI 0.63–2.52), 1.04 for subjects with recent use (95% 0.44–2.41), and 0.8 for subjects with past use (95% CI 0.64–1.01), compared with never use. Alcohol-related disease (adjusted OR 1.39; 95% CI 1.13–1.71), biliary stone (adjusted OR 1.44; 95% CI 1.24–1.68), and chronic kidney disease (adjusted OR 1.27; 95% CI 1.06–1.51) were other factors related to pyogenic liver abscess.

5.3. Risk of Pyogenic Liver Abscess Associated with Cumulative Duration of Selective Serotonin Reuptake Inhibitors Use

In further analysis, the adjusted OR of pyogenic liver abscess was 1.01 for subjects with increasing cumulative duration of SSRIs use for each additional month of use (95% CI 0.99–1.02), compared with never use (Table 3). There was no duration-dependent effect of SSRIs use on the risk of pyogenic liver abscess.

Table 2: Odds ratio and 95% confidence interval of pyogenic liver abscess associated with selective serotonin reuptake inhibitors use, non-selective serotonin reuptake inhibitor antidepressants use, and comorbidities by logistical regression model

	Crude		Adjusted†	
Variable	OR	(95% CI)	OR	(95% CI)
Sex (male vs. female)	1.00	(0.90, 1.12)		
Age (per one year)	1.00	(0.99, 1.00)		
Selective serotonin reuptake inhibitors (never use as a reference)				
Current use	1.31	(0.66, 2.61)	1.26	(0.63, 2.52)
Recent use	1.08	(0.46, 2.50)	1.04	(0.44, 2.41)
Past use	0.82	(0.66, 1.04)	0.80	(0.64, 1.01)
Ever use of non-selective serotonin reuptake inhibitor antidepressants (never use as a reference)	0.98	(0.87, 1.10)		
Comorbidities before index date (yes vs. no)				
Alcohol-related disease	1.34	(1.09, 1.65)	1.39	(1.13, 1.71)
Biliary stone	1.41	(1.21, 1.64)	1.44	(1.24, 1.68)
Chronic kidney disease	1.22	(1.02, 1.45)	1.27	(1.06, 1.51)
Chronic liver disease	1.11	(0.99, 1.24)		
Diabetes mellitus	1.10	(0.98, 1.23)		

†Variables found to be statistically significant in the univariable model were further included in the multivariable logistic regression model. Additionally, adjusted for alcohol-related disease, biliary stone, and chronic kidney disease

6. Discussion

In this case-control study, we did not find a significant association between PLA risk and SSRIs use (Table 2) and a duration-dependent effect between PLA risk and SSRIs use (Table 3). We also noted that alcohol-related disease, biliary stone, and chronic kidney disease were other factors related to pyogenic liver abscess, although no actual risk factors for acquiring PLA was found in previous studies [39]. To the best of our knowledge, this is the first case-control study to explore the relationship between PLA and SSRIs worldwide. Although the results revealed no association between PLA and SSRIs, its clinical implications were important, which provided the local physicians and psychiatrists more information about PLA and relative drug use. We could hypothesize temporarily that SSRIs use is not associated with PLA risk, and all antidepressants drugs do not have an association

with risk for developing PLA. More and ideal research is needed to examine the risk of PLA and another kind of antidepressants use in Taiwan, and even worldwide in the future.

Table 3: Risk of pyogenic liver abscess associated with cumulative duration of selective serotonin reuptake inhibitors use

Variable	Case number / control number	Crude odds ratio	(95% CI)	Adjusted odds ratio†	(95% CI)
Never use of selective serotonin reuptake inhibitors as a reference	1632/6022	1.00	(reference)	1.00	(reference)
Cumulative duration of selective serotonin reuptake inhibitors use (increase in duration for every one month)	117/496	1.01	(0.99, 1.02)	1.01	(0.99, 1.02)

†Variables found to be statistically significant in the univariable model were further included in the multivariable logistic regression model. Additionally adjusted for alcohol-related disease, biliary stone, and chronic kidney disease

7. Limitation

Some limitations need to be further discussed. First, the actual risk factors for PLA are unknown and populations with PLA are most often diagnosed when hospitalized [12, 39, 40]. Maybe it is not appropriate to examine the relationship between PLA risk and of SSRIs by just the use of NHI data only, which might result in distortion. Second, owing to the inherent limitation of only the database use, and we could not ensure the compliance of enrolled patients for following the treatment plan. The NHI database enables only 6 diagnoses for each case and physician's individual opinions, coding of diagnosis might be biased if patients has more than six underlying diseases. Third, there might be deficiency in microbiological data from NHI database, which might not reflect accurate condition in the general population. Lastly, there were the inherent limitations of case-control study, which besides being observational, also involves recall bias or selection bias when exploring association between use of SSRIs and diagnosis of PLA.

8. Strength

This is an interesting, novel and first case-control study in the world, to examine the association between PLA and SSRIs. All comorbidities were diagnosed based on ICD-9 codes, which have been well validated in previous studies.[14, 28-38] This study also had a large sample size with excellent statistical power resulting from use of large database from the Taiwan National Health Insurance Program that has contributed much to the epidemiological research in the past years in Taiwan, and is more convincing to the all readers.

9. Conclusion

No significant association between PLA risk and SSRIs use was found in the study. There was also no duration-dependent effect of SSRIs use on PLA risk. Further research and trials are needed to explore and confirm the study findings. Close collaboration among clinical physicians, research scientists, and public health workers is indeed necessary for exploring the complex relationship between PLA, comorbidities and SSRIs in the future.

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