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Association of Proton Pump Inhibitor/Histamine2 Blocker Use and Ocular Toxoplasmosis: Findings from a Large U.S. National Database

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Abstract

Objective: To test the hypothesis that PPI use is associated with an increased risk of being diagnosed with toxoplasmic retinochoroiditis

Design: Retrospective, matched case-control study using data from 2000–2020

Participants: Cases of ocular toxoplasmosis and controls were matched 5:1 for age, gender, race, with eligibility date ±3 months from index date of exposed match. Exclusion occurred for being <18 years old, having congenital toxoplasmosis, having <2 years in the insurance plan prior to the index date and not having at least one visit to an eyecare provider prior to the index date.

Methods: Cases of ocular toxoplasmosis were identified using ICD 9/10 codes and PPI use or diseases highly associated with PPI were identified utilizing national drug codes from an administrative medical claims database.

Main Outcome Measures: The primary outcome was defined as having a prescription for PPI or H2 blocker. Multivariable logistic regression analyses were performed controlling for demographic and systemic health variables.

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Conflicts of Interest:

Brian VanderBeek has a consulting contract with EyePoint Pharmaceuticals Mark Johnson serves on Independent Data Monitoring Committees for Aura Biosciences and Amgen (not related to current work) No other conflicts exist

Results: 4069 cases and 19177 controls met eligibility criteria. 24.3% (989/4069) of ocular toxoplasmosis cases were on PPI/H2 blockers compared to 19.2% (3763/19177) of controls. An adjusted logistic regression model demonstrated 1.28 greater odds of PPI/H2 blocker use in ocular toxoplasmosis cases compared to matched controls (95% CI: 1.17–1.40, $p < 0.001$).

Conclusions: PPI/H2 blocker exposure was associated with an increased risk of being diagnosed with ocular toxoplasmosis, corroborating findings from a prior case series.

Keywords

toxoplasmosis; retinochoroiditis; uveitis; proton pump inhibitors; histamine2 blockers

Introduction

Toxoplasma gondii is a ubiquitous, obligate intracellular protozoan that sexually reproduces in felines but can infect most warm-blooded animals. The parasite is most commonly acquired following contact with infected fecal matter of cats, undercooked meats, or contaminated water.[1,2] In humans, congenital infection may result in subclinical presentations, induce stillbirths, or lead to the development of the classic triad of bilateral retinochoroiditis, hydrocephalus, and intracranial calcifications.[2] In contrast to congenital disease, most acquired infections in adults are asymptomatic; however, approximately 2% of immunocompetent adults will develop ocular complications, typically a unilateral, unifocal area of necrotizing retinochoroiditis with overlying dense vitritis, after exposure to the pathogen.[3] This is in contrast to immunocompromised patients in which acquired ocular disease may be bilateral and multifocal with systemic manifestations ranging from a flu-like illness to encephalitis, seizures, and death.[4] With high seroprevalence rates of toxoplasmosis in humans and wild animals worldwide, it remains the most common cause of infectious posterior uveitis and a significant healthcare burden.[2]

We previously reported in a small, retrospective case series that 3 of 7 otherwise healthy patients that developed toxoplasmic retinochoroiditis following exposure to wild game were using antacids and/or protein pump inhibitors (PPIs) for acid reflux.[5] This rate of usage of PPIs appeared to be higher than prior general population estimates in the United States of approximately 20%.[6] PPIs are the most effective gastric acid-suppressing agents on the market and are first line therapy for treatment of many gastric acid-related disorders. While they are relatively well tolerated in the short term, prolonged use has been associated with *Clostridium difficile* infections, community acquired pneumonia, micronutrient deficiencies, and kidney dysfunction among others.[7] The underlying mechanism is unclear in these associations; however, there has been speculation that the increased risk of infection while using these medications, whether it be *C. difficile* or community acquired pneumonia, is related to gut flora changes and/or impaired immune cell function.[7] Thus, we hypothesized that the use of PPIs increased susceptibility to the acquisition of acquired toxoplasmic retinochoroiditis in lieu of our original observation and the associated risks of acquisition of other infectious organisms.

In order to test this hypothesis, we reviewed a large healthcare claims database using ICD-9 and −10 codes and identified all adult patients who were diagnosed with new toxoplasmic

retinochoroiditis infections and compared them with matched controls for previous history of PPI use or having an ailment likely to be associated with PPI use.

Methods

Dataset

Data were abstracted from Optum's de-identified Clinformatics® Data Mart Database. The database contains all outpatient medical claims (office visits, procedures, and medications given) as well as demographic data and some laboratory values for all patients enrolled in commercial and Medicare Advantage insurance plans. The subset of data available for this study included all patients in the database from January 1, 2000, to June 30, 2020. The institutional review board of the University of Pennsylvania deemed this study exempt from review due to the de-identified nature of the data.

Cases and Controls

All patients over 18 years old with a diagnosis of toxoplasmosis ocular infection were identified using ICD9 and ICD10 codes (please see Supplemental Table 1 for all codes used in this study). The index date was set to the earliest date of toxoplasmosis diagnosis. Patients were excluded for having ≤2 years in the insurance plan or not having an eye exam prior to the index date. Also, exclusion occurred for any diagnosis of congenital toxoplasmosis at any point during their time in the plan. As many as 5 controls were selected for every case and matched on age (±3 years), gender, race and insurance start date (±3 months). Each control was assigned the index date of the matched case and required to meet the same exclusion criteria as controls.

Analysis and Covariates

The primary outcome was the odds of having filled a prescription for a PPI or H2 blocker prior to the index date. Multivariable logistic regression was used to determine the odds of having a gastric hyperacidic condition. Covariates used in the model were several demographic and systemic health variables, including alcohol abuse, smoking, prescription nonsteroidal anti-inflammatories, oral steroids, or pregnancy in the 2 years prior to the index date[8] (see Table 1 for the full list of covariates). Two sensitivity analyses were run, including one that broadened the definition of the primary outcome to also include either filling a prescription for a PPI/H2 blocker or having a diagnosis that would likely to lead to PPI/H2 blocker use (esophagitis, gastritis, etc.; please see Supplemental Table 1 for the full list of diagnoses used). The other analysis included all toxoplasmosis diagnoses that did not specify ocular disease.

Results

Four thousand and sixty-nine cases of toxoplasmic retinochoroiditis and 19177 unaffected, matched controls met all inclusion/exclusion criteria (Table 1). Cases and controls were similar in age (54.1 years old (standard deviation±18.1) vs. 54.3 (SD±18.2), respectively), gender composition (39.2% male vs. 39.1%) and racial mixture (62.3% White vs. 62.5%). Of ocular toxoplasmosis cases, 24.3% (989/4069) were on PPI/H2 blockers compared to

19.2% (3763/19177) of controls. After adjusting for all covariates of interest, primary analysis showed a an increased odds ratio of 1.28 (95% CI: 1.17–1.40, p<0.001) for known PPI use among toxoplasmosis cases (Table 2).

For the sensitivity analysis with a broader definition to also include those with diseases likely lead to PPI/H2 blocker use, 40.2% (1636/4069) of the toxoplasmosis cases and 34.9% (6684/19177) of controls had exposure. After multivariable analysis, the odds of having exposure more broadly defined was 1.20 (95% CI: 1.11–1.30, p<0.001) for the toxoplasmosis cases versus controls. The other sensitivity analysis which broadened the definition of cases to all patients diagnosed with ocular or systemic toxoplasmosis included 4931 cases and 23293 matched controls. After multivariable analysis the odds of a toxoplasmosis case having a filled a prescription for a PPI/H2 blocker was again higher at 1.23 (95% CI: 1.13–1.33, p<0.001) (Table 3).

Discussion

We evaluated 4069 cases of ocular toxoplasmosis and compared them to matched controls to find that cases were at significantly elevated odds of having filled a prescription for a PPI or H2 blocker prior to the date of the toxoplasmosis diagnosis. When sensitivity analyses were run to test assumptions made in the case and outcome definitions, our findings were essentially unchanged, suggesting a robust association. Together, these findings are consistent with our hypothesis that PPI/H2 blocker use increases the risk of toxoplasmosis infection.

It is likely that PPIs may be only one of many risk factors for the development of ocular toxoplasmosis in adults. There are previously reported environmental and behavioral risk factors that have been associated with developing systemic toxoplasmosis. Such factors include living at lower elevations, having contact with raw meat, consuming unfiltered water or unpasteurized milk, and living in a community with an increased density of cats.[1,9] Similarly, severity and recurrences of ocular toxoplasmosis have been positively correlated with increasing age and the use of steroids without concurrent antibiotics.[10–12] These host risk factors do not include pathogen-associated attributes such as tropism of certain *T. gondii* strains to the eye and the pathogen's expression of specific neuroinvasive genes that have been associated with ocular complications.[13] However, we are unaware of prior reports identifying PPI use as a potential risk factor for developing toxoplasmic retinochoroiditis. It is unclear at this time whether this finding is simply due to an increased risk of developing acquired infections or if this finding is specific to ocular disease alone.

While the pathogenic mechanism underlying this association is unclear, PPIs are known to significantly reduce gastric acid levels, thereby increasing gut pH. Omeprazole, an over-the-counter PPI, has been shown to inhibit acidification of phagolysosomes *in vitro*.[14,15] *T. gondii* tachyzoites are extremely susceptible to acidic conditions (low pH) and acidification of the phagosome is one of the primary defense mechanisms of the host innate immune response to toxoplasmosis invasion.[16] Taken together, we hypothesize that the reduction in gut acidity and neutralization of the phagolysosome resulting from PPI use may be responsible for the increased risk of being diagnosed with toxoplasmic retinochoroiditis. In

further support of this hypothesis and the importance of pH changes in the host-pathogen interplay is the observation that *T. gondii* has evolved specific mechanisms to inhibit acidification and fusion of the phagosome to other endocytic cellular compartments.[17,18] Thus, control of pH changes are central to both host defense and *T. gondii* invasiveness.

Our retrospective, population-based study has several strengths and weaknesses. The size of our patient population is substantial, including over 4,000 cases of ocular toxoplasmosis and 19,000 matched controls in the United States. This large patient population allowed us to identify a new, potential risk factor for the diagnosis of ocular toxoplasmosis that could not have been recognized in smaller cohorts. Nevertheless, we acknowledge that retrospective analyses cannot prove causality and that ICD-based studies are limited by proper use of diagnostic codes. Further, it is unclear what impact specific strains or clades of *T. gondii* may have on our reported association. This consideration would be especially important in places such as Brazil, where rates of toxoplasmic retinochoroiditis are higher and predominant toxoplasmosis strains differ from those found in the United States.[2,13,19] Lastly, it should be noted that PPIs became readily available in over-the-counter formulations in 2003, and PPI usage was likely underestimated in both cases and controls in our study due to the inability of claims data to capture over-the-counter medication uses. Despite this, there is no reason to believe that an impactful differential in exposure measurement would have occurred across the study groups, since both groups had exposure defined by prescription fill and/or associated diagnoses.

In summary, we found that receiving a diagnosis of ocular toxoplasmosis was associated with increased odds of having filled a PPI and/or H2 blocker prescription prior to the diagnosis. Future work should be directed at elucidating the mechanism by which PPI or H2 blocker use can increase the risk of toxoplasmosis infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Brian VanderBeek had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Precis

Toxoplasmic retinochoroiditis is the most common cause of infectious posterior uveitis. In the following manuscript, we show that proton pump inhibitor/histamine2 blocker use is associated with the diagnosis of the condition.

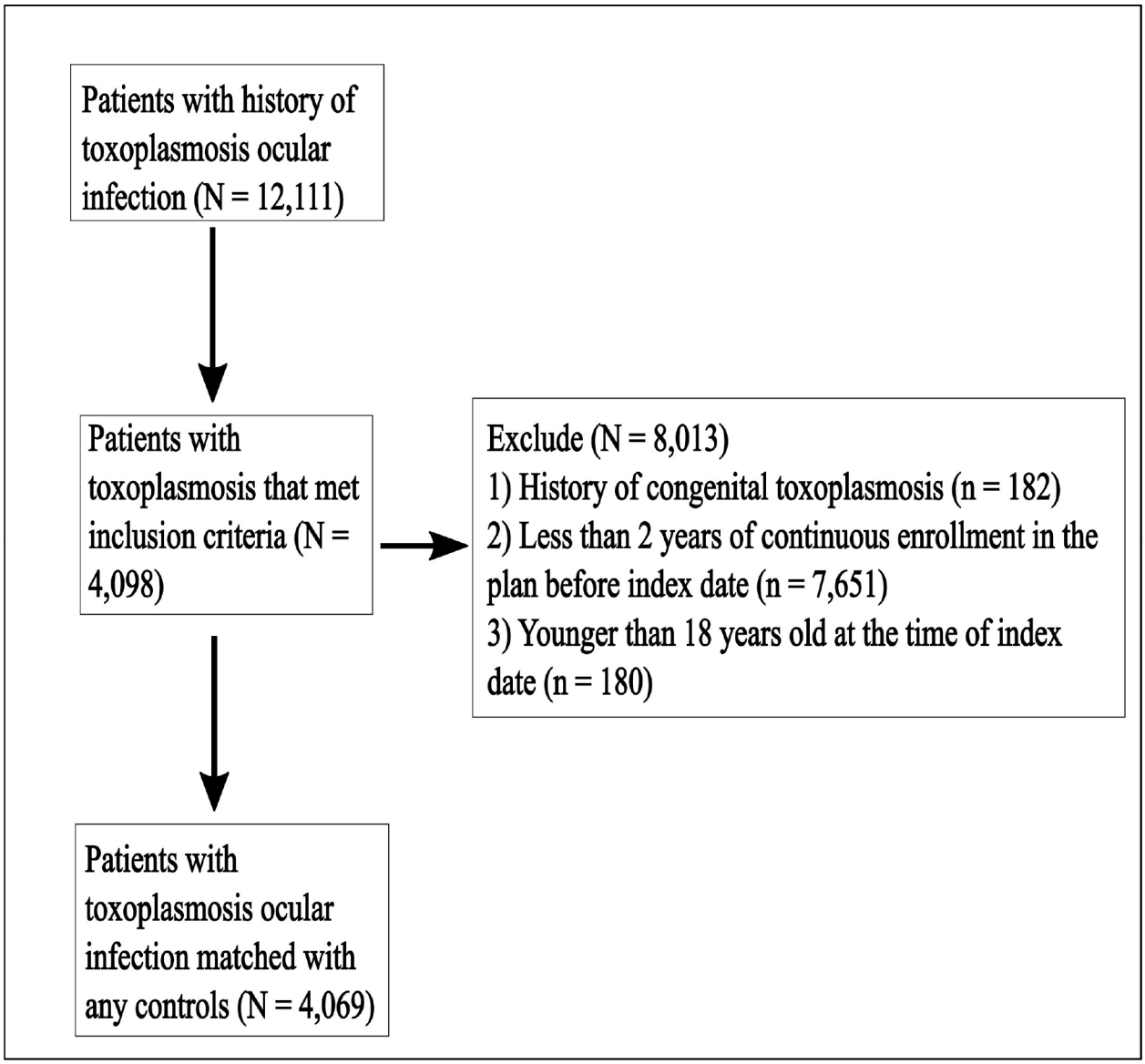

Figure 1:
Study design

Table 1:

Descriptive of the study cohort for the primary analysis

	Control (N=19177)	Case (N=4069)
Age (years)		
N	19177	4069
Mean (SD)	54.3 (18.2)	54.1 (18.1)
Median	54.0	54.0
Q1, Q3	39.0, 70.0	39.0, 70.0
Range	(18.0–90.0)	(18.0–90.0)
Gender		
Male	7495 (39.1%)	1596 (39.2%)
Female	11677 (60.9%)	2472 (60.8%)
Unknown	5 (0.0%)	1 (0.0%)
Race/Ethnicity		
White	11979 (62.5%)	2536 (62.3%)
Black	2096 (10.9%)	441 (10.8%)
Hispanic	2773 (14.5%)	591 (14.5%)
Asian	653 (3.4%)	138 (3.4%)
Unknown	1676 (8.7%)	363 (8.9%)
Education level		
Less than or equal to HS Diploma	4387 (22.9%)	1073 (26.4%)
Less than Bachelor Degree	9558 (49.8%)	1873 (46.0%)
Bachelor Degree Plus	4009 (20.9%)	874 (21.5%)
Unknown	1223 (6.4%)	249 (6.1%)
Household income		
<$40K	3016 (15.7%)	679 (16.7%)
$40K – $49K	1005 (5.2%)	217 (5.3%)
$50K – $59K	1140 (5.9%)	212 (5.2%)
$60K – $74K	1632 (8.5%)	334 (8.2%)
$75K – $99K	2309 (12.0%)	480 (11.8%)
$100K+	5469 (28.5%)	1072 (26.3%)
Unknown	4606 (24.0%)	1075 (26.4%)
Geographic location		
Upper Midwest	5189 (27.1%)	752 (18.5%)
Southern Midwest	3254 (17.0%)	639 (15.7%)
Northeast	2373 (12.4%)	668 (16.4%)
Mountain	1512 (7.9%)	262 (6.4%)
Pacific	1983 (10.3%)	407 (10.0%)
South Atlantic	4835 (25.2%)	1328 (32.6%)
Unknown	31 (0.2%)	13 (0.3%)
History of hypertension		
No	9756 (50.9%)	2027 (49.8%)

	Control (N=19177)	Case (N=4069)
Yes	9421 (49.1%)	2042 (50.2%)
History of hypercholesterolemia		
No	8538 (44.5%)	1772 (43.5%)
Yes	10639 (55.5%)	2297 (56.5%)
Ischemic heart disease		
No	16117 (84.0%)	3292 (80.9%)
Yes	3060 (16.0%)	777 (19.1%)
Heart failure		
No	17902 (93.4%)	3753 (92.2%)
Yes	1275 (6.6%)	316 (7.8%)
Diabetes Mellitus		
No	14669 (76.5%)	3089 (75.9%)
Yes	4508 (23.5%)	980 (24.1%)
Alcohol Abuse		
No	18687 (97.4%)	3944 (96.9%)
Yes	490 (2.6%)	125 (3.1%)
Smoking		
No	15596 (81.3%)	3236 (79.5%)
Yes	3581 (18.7%)	833 (20.5%)
Pregnancy in the 2 years prior to index date		
No	18366 (95.8%)	3678 (90.4%)
Yes	811 (4.2%)	391 (9.6%)
NSAID use in the 2 years prior to the index date		
No	15762 (82.2%)	3238 (79.6%)
Yes	3415 (17.8%)	831 (20.4%)
Oral steroid use in the 2 years prior to the index date		
No	15715 (81.9%)	3114 (76.5%)
Yes	3462 (18.1%)	955 (23.5%)
A prescription for PPI or H2 blocker		
No	15504 (80.8%)	3080 (75.7%)
Yes	3673 (19.2%)	989 (24.3%)
A prescription for PPI or H2 blocker OR hx of a disease that would be likely to lead to use of a PPI/H2 blocker		
No	12493 (65.1%)	2433 (59.8%)
Yes	6684 (34.9%)	1636 (40.2%)

H2, histamine; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump in inhibitor

Table 2:

Association of H2/PPI use with diagnosis of ocular toxoplasmosis for the primary analysis

	Control	Case	aOR (95% CI)*	P value
A prescription for PPI/H2 blocker	3673 (19.2%)	989 (24.3%)	1.28 (1.17, 1.40)	<0.001
A prescription for PPI/H2 blocker OR hx of disease that would be likely to lead to use of PPI/H2 blocker	6684 (34.9%)	1636 (40.2%)	1.20 (1.11, 1.30)	<0.001

*Conditional logistic regression adjusting for age, education, income, geographic location, hypertension, hypercholesterolemia, Ischemic heart disease, Heart failure, Diabetes Mellitus, Alcohol Abuse, Smoking, Pregnancy in the 2 years prior to index date, NSAID use in the 2 years prior to the index date and oral steroid use in the 2 years prior to the index date

aOR, adjusted odds ratio; CI, confidence interval; H2, histamine; hx, history; PPI, proton pump inhibitor

Table 3:

Association of H2/PPI use with diagnosis of ocular toxoplasmosis for the sensitivity analysis

	Control	Case	aOR (95% CI)*	P value
A prescription for PPI/H2 blocker	4557 (19.6%)	1199 (24.3%)	1.23 (1.13, 1.33)	<0.001
A prescription for PPI/H2 blocker OR hx of disease that would be likely to lead to use of PPI/H2 blocker	8152 (35.0%)	1997 (40.5%)	1.19 (1.11, 1.28)	<0.001

*Conditional logistic regression adjusting for age, education, income, geographic location, hypertension, hypercholesterolemia, Ischemic heart disease, Heart failure, Diabetes Mellitus, Alcohol Abuse, Smoking, Pregnancy in the 2 years prior to index date, NSAID use in the 2 years prior to the index date and oral steroid use in the 2 years prior to the index date

aOR, adjusted odds ratio; CI, confidence interval; H2, histamine; hx, history; PPI, proton pump inhibitor