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Association Between Neonatal Urinary Tract Infection and Risk of Childhood Allergic Rhinitis

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Abstract: The current population-based study investigated the onset of neonatal urinary tract infection (UTI) and the associated risks of allergic rhinitis.

From 2000 to 2005, 3285 children with neonatal UTI and 13,128 randomly selected controls were enrolled from the National Health Insurance Research Database in Taiwan and frequency matched by gender, urbanization of residential area, parental occupation, and baseline year. We compared the risk of allergic rhinitis between the non-UTI and UTI cohorts by performing multivariable Cox regression analysis.

We observed a significant relationship between UTI and allergic rhinitis. This study examined 16,413 patients, among whom 3285 had UTI and 13,128 did not have UTI. The overall incidence rate ratio of allergic rhinitis was 1.41-fold higher in the UTI cohort than in the non-UTI cohort (100.2 vs 70.93 per 1000 person-y). After potential risk factors were adjusted for, the adjusted hazard ratio of allergic rhinitis was 1.32 (95% confidence interval = 1.23–1.41). Regardless of gender, the UTI cohort had a higher risk of allergic rhinitis than that of the non-UTI cohort. The patients with UTI in different follow-up durations were equally susceptible to developing allergic rhinitis compared with those without UTI, especially in follow-up durations shorter than 5 years. Patients with UTI and particular comorbidities such as infections and neonatal jaundice had a significantly increased risk of allergic rhinitis.

UTI in newborns is significantly associated with the development of allergic rhinitis in childhood and might be a risk factor for subsequent childhood allergic rhinitis.

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Abbreviations: CI = confidence interval, HR = hazard ratio, ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification, NHIRD = National Health Insurance Research Database, UTI = urinary tract infection.

INTRODUCTION

Allergic rhinitis is a common allergic disease affecting ~10% to 25% of the global population.[1] This evidence clearly suggests that allergic rhinitis is influenced by genetic and environmental factors.[2] Numerous studies have investigated the role of environmental factors, such as air pollution, changed lifestyle, and bacterial and viral infections, in the development of allergic rhinitis.[2–5] According to the hygiene hypothesis, infections can influence the immature immune system and induce an immune response toward the T helper 1 phenotype, thereby reducing the risk of developing allergic disease.[6,7] However, lower respiratory tract infections, including respiratory syncytial virus bronchiolitis, pneumonia, measles, and possibly pertussis, in childhood might increase the subsequent risk of childhood asthma.[8] In addition, several studies have suggested that early exposure to infections in utero or early in life is potentially a critical risk factor for the development of allergic disease.[9–12] Based on a review of the literature, no studies have investigated whether neonatal non-respiratory bacterial infection, such as neonatal urinary tract infection (UTI), is associated with the risk of childhood allergic rhinitis.

We hypothesized that neonatal UTI is a risk factor for childhood allergic rhinitis. We conducted a population-based retro-spective cohort study to investigate the association between neonatal UTI and the subsequent risk of allergic rhinitis by

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I-CL and C-HK equally contributed to this study.

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analyzing data from the Taiwan National Health Insurance Research Database (NHIRD).

METHODS

Data Source

This study applied a retrospective cohort study design. We identified illnesses according to International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code 5990 or 77182 for the period 2000 to 2005. The UTI cohort comprised 3285 children newly diagnosed with UTI and aged younger than 1 month. The date of the first UTI diagnosis was the baseline index date. We used 2 matching methods, frequency and propensity score matching, to select the comparison cohort patients. First, for each child with UTI, we randomly selected 4 patients without medical claims for UTI care and frequency matched them with the UTI patients according to gender, urbanization of residential area, parental occupation, and baseline year. Second, we corrected for various risk factors in the 2 cohorts by using propensity score matching at a 1:4 ratio.

We classified the 316 cities and townships in Taiwan into 7 ordered levels of urbanization based on scores of population density (people/km^2), the proportion of people with higher education, the elderly and agricultural population, and the number of physicians per 100,000 people. The number of patients was low in the Level 6 and 7 classifications; therefore, we combined them with the Level 5 patients. The highest urbanization level was Level 1, whereas Level 4 was the lowest. The patients' family were classified according to occupation as white collar (including civil servants, institution workers, and enterprise, business, and industrial administration personnel), blue collar (including farmers, fishermen, vendors, and industrial laborers), and others (including retired, unemployed, and low-income patients). Patients with a history of UTI and missing data on date of birth or gender at the baseline were excluded from this study. The follow-up person-years for each patient were calculated from the index date until a diagnosis of allergic rhinitis (ICD-9-CM code 477), withdrawal from the insurance system, the end of 2008, or censoring because of death or loss to follow-up. The mean follow-up duration for the study patients was 5.21 person-years (standard deviation = 2.37).

In addition, we reviewed the history of comorbidities for each patient before the index date, namely infections (ICD-9-CM code 771), neonatal jaundice (ICD-9-CM code 774), preterm low birth weight (ICD-9-CM codes 764 and 765), other fetal and newborn respiratory conditions (ICD-9-CM code 770), and vesicoureteral reflux (VUR) (ICD-9-CM code 593.7), for adjusting for the risk of allergic rhinitis.

Ethics Statement

The NHIRD encrypts patient personal information to protect privacy and provides researchers with anonymous identification numbers associated with relevant claims information, including gender, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was exempted from review by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2–115). The IRB also specifically waived the consent requirement.

Statistical Analysis

The distinct demographic variables and comorbidity histories between the UTI and non-UTI cohorts were verified by conducting a chi-square test and Student's *t* test. When the assumption of the chi-square test was violated, we used Fisher's exact test to test the categorical variables. We calculated the incidence of allergic rhinitis stratified according to gender, comorbidity, and follow-up duration in the non-UTI and UTI cohorts. We compared the incidence of allergic rhinitis between the non-UTI and UTI cohorts by using Poisson regression analysis. In addition, the incidence rate ratios (IRRs) and 95% confidence intervals (CIs) were obtained. After the potential variables were controlled, the adjusted hazard ratios (HRs) and 95% CIs of allergic rhinitis between the non-UTI and UTI cohorts were obtained by conducting multivariable Cox regression analysis. In addition, the interaction effect between UTI and risk factors, such as gender and comorbidity, was estimated by conducting multivariable Cox regression analysis. The propensity score was calculated using a logistic regression to estimate the probability of UTI assignment, according to baseline variables including the year of UTI development, gender, urbanization of residential area, parental occupation, and history of comorbidity. After propensity score matching, we used Cox proportional hazards model stratification of the matched pairs to estimate the difference in the risk of allergic rhinitis between the UTI and non-UTI cohorts. A P value < 0.05 obtained through 2-tailed tests indicated statistical significance.

Data analyses were performed using the SAS 9.3 statistical package (SAS Institute Inc., Cary, NC). In addition, we used R software (R Foundation for Statistical Computing, Vienna, Austria) to conduct a Kaplan–Meier analysis for measuring the cumulative allergic rhinitis of both study cohorts and then used the log-rank test to evaluate the differences between the 2 cumulative incidence curves.

RESULTS

This study examined 16,413 patients, among whom 3285 had UTI and 13,128 did not have UTI (Table 1). The mean age of the patients was nearly 15 days in both cohorts. The demographic characteristics of the 2 cohorts had similar distributions: the patients were predominantly boys (57.6%), their residential areas were characterized by a high level of urbanization (53.0%), and parental occupation was mainly white collar (58.1%). The UTI cohort exhibited more prevalent comorbidities before the index date than the non-UTI cohort did. The comorbidities comprised infections (37.1% vs 2.77%), neonatal jaundice (36.8% vs 6.03%), preterm low birth weight (5.39% vs 2.92%), other fetal and newborn respiratory conditions (4.02% vs 2.31%), and VUR (2.19% vs 0.00%).

As Table 2 shows, the overall incidence rates of allergic rhinitis were 100.2 per 1000 person-years and 70.93 per 1000 person-years in the UTI cohort and non-UTI cohort, respectively. The IRR of allergic rhinitis was 1.41-fold (95% CI = 1.32–1.51) higher in the UTI cohort than in the non-UTI cohort, and the adjusted HR of allergic rhinitis was 1.32 (95% CI = 1.23–1.41), after adjustment for potential risk factors.

The IRR of allergic rhinitis was 1.42-fold higher in girls with UTI than in those without UTI (incidence rate: 87.29 vs 61.29 per 1000 person-y). In addition, the IRR of allergic rhinitis was 1.41-fold higher in boys with UTI than in those without UTI (incidence rate: 110.4 vs 78.49 per 1000 person-y). Regarding the gender-specific risk analysis for both cohorts, the adjusted HR of allergic rhinitis was 1.34 (95% CI = 1.19–1.51) for girls and 1.31 (95% CI = 1.20–1.43) for boys. Comorbidity-related analysis revealed that the adjusted HR of allergic rhinitis was 1.43 (95% CI = 1.31–1.55) for patients in the UTI cohort without comorbidity and 1.18 (95% CI = 1.06–1.32) for patients in the UTI

TABLE 1. Comparison of Demographics and Comorbidity Between with Urinary Tract Infection (UTI) and Without Urinary Tract Infection (Non-UTI) Cohorts

	Urinary Tract Infection				
	No (N = 13,128) n	**Yes (N = 3285) %**	**n**	**%**	***P***
Gender					0.98
Girls	5566	42.4	1392	42.4	
Boys	7562	57.6	1893	57.6	
Age, days, mean (SD)*	14.6 (9.02)		13.8 (9.27)		<0.0001
Urbanization					0.98
1 (highest)	2895	22.0	724	22.0	
2	4072	31.0	1018	31.0	
3	2600	19.8	652	19.9	
4	2055	15.7	520	15.8	
5 (lowest)	1506	11.5	371	11.3	
Occupation					0.98
White collar	7628	58.1	1907	58.1	
Blue collar	3352	25.5	840	25.6	
Others	2148	16.4	538	16.4	
Comorbidity					
Infections	363	2.77	1220	37.1	<0.0001
Neonatal jaundice	791	6.03	1210	36.8	<0.0001
Preterm low birth weight	383	2.92	177	5.39	<0.0001
Other fetal and newborn respiratory conditions	303	2.31	132	4.02	<0.0001
Vurvesicoureteral reflux†	0	0.00	72	2.19	<0.0001

Chi-square test. UTI = urinary tract infection. Urbanization: level 1 is the most urbanized; level 5 is the least urbanized. White collar: civil services, institution workers, enterprise, business, and industrial administration personnel; blue collar: farmers, fishermen, vendors, and industrial laborers; others: retired, unemployed, and low-income populations.

* Student's *t* test.

† Fisher's exact test.

TABLE 2. Incidence and Adjusted Hazard Ratio of Allergic Rhinitis Stratified by Gender, Comorbidity, and Follow-up Year Compared Between Non-UTI and UTI Cohorts

	Urinary Tract Infection							
	No			Yes			Compared to Non-UTI	
Variables	**Event**	**PY**	**Rate**	**Event**	**PY**	**Rate**	**IRR (95% CI)**	**Adjusted HR (95% CI)**
Overall	4704	66,318	70.93	1495	14921	100.2	1.41(1.32–1.51)***	1.32 (1.23–1.41)***
Gender								
Girls	1786	29,140	61.29	574	6576	87.29	1.42(1.28–1.59)***	1.34(1.19–1.51)***
Boys	2918	37,178	78.49	921	8345	110.4	1.41(1.29–1.54)***	1.31(1.20–1.43)***
Comorbidity								
No	4176	60,282	69.27	589	5927	99.38	1.43(1.30–1.59)***	1.43(1.31–1.55)***
Yes	528	6036	87.47	906	8995	100.7	1.15(1.01–1.31)*	1.18(1.06–1.32)**
Follow, year								
<1	824	12,725	64.75	347	3103	111.8	1.73(1.58–1.89)***	1.66(1.43–1.93)***
1–3	1744	22,769	76.59	563	5249	107.3	1.40(1.28–1.53)***	1.32(1.17–1.48)***
3–5	1486	17,686	84.02	430	17686	111.0	1.32(1.20–1.46)***	1.20(1.05–1.37)**
≥5	650	13,138	49.48	155	2696	57.48	1.16(1.01–1.34)*	1.13(0.92–1.39)

95% CI = 95% confidence interval, Adjusted HR = adjusted hazard ratio, IRR = incidence rate ratio, PY: Person-years, Rate: incidence rate, per 1000 person-years, UTI = urinary tract infection. Multiple analysis including age, gender, urbanization, occupation, and history of comorbidity.

* $P < 0.05$.

** $P < 0.01$.

*** $P < 0.001$.

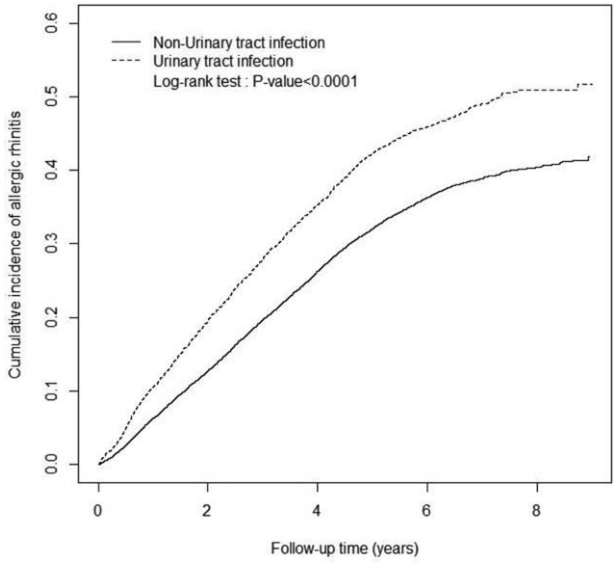

FIGURE 1. Cumulative incidence of allergic rhinitis among patients with urinary tract infection (UTI) (dashed line) and those without urinary tract infection (non-UTI) (solid line).UTI = urinary tract infection.

cohort with comorbidity, compared with those in the non-UTI cohort. The patients with UTI in different follow-up durations were equally susceptible to developing allergic rhinitis compared with the patients without UTI, except during a follow-up time of 5 years or more (adjusted HR at <1 y of follow-up = 1.66, 95% CI = 1.43–1.93; adjusted HR at 1–3 y of follow-up = 1.32, 95% CI = 1.17–1.48; adjusted HR at 3 to 5 y of follow-up = 1.20, 95% CI = 1.05–1.37). By the end of the follow-up period, the cumulative incidence of allergic rhinitis was 10.5% higher in the UTI cohort than in the non-UTI cohort (50.9% vs 40.4%) (Figure 1).

Table 3 shows the interaction between UTI and gender or different comorbidities. The adjusted HR of allergic rhinitis was 1.67 (95% CI = 1.53–1.82) in boys with UTI, 1.32 (95% CI = 1.20–1.47) in girls with UTI, and 1.27 (95% CI = 1.20–1.34) in boys without UTI, compared with girls without UTI (P value = 0.8636 for interaction). Compared with non-UTI patients without comorbidity, the adjusted HR of allergic rhinitis was 1.25 (95% CI = 1.14–1.37) in non-UTI patients with comorbidity, 1.43 (95% CI = 1.30–1.55) in UTI patients without comorbidity, and 1.45 (95% CI = 1.35–1.56) in UTI patients with comorbidity (P value = .0017 for interaction).

Interactions of comorbidities including infections (interaction P value = 0.0380), preterm low birth weight (interaction P value = .0085), and other fetal and newborn respiratory conditions (interaction P value = .0420) were associated with a higher risk of allergic rhinitis in the UTI cohort than in the non-UTI cohort.

Propensity score matching analysis was applied for bias reduction in the investigation of the association between allergic rhinitis outcomes and UTI. There were 1485 patients in the UTI cohort and 5940 patients in the non-UTI cohort (Supplementary Table 1, http://links.lww.com/MD/A427). The baseline potential risk in the 2 cohorts did not significantly differ ($P > 0.05$). When we used propensity score matching, the UTI cohort still had a higher risk of allergic rhinitis than that of the non-UTI cohort (adjusted HR = 1.39, 95% CI = 1.27–1.53; Supplementary Table 2, http://links.lww.com/MD/A427). The UTI patients had a greater risk of developing allergic rhinitis than that of the non-UTI patients, especially when they had infections or neonatal jaundice.

DISCUSSION

Based on a review of the literature, this is the first population-based case–control study to demonstrate an association between neonatal UTI and a risk of childhood allergic rhinitis. This association was independent of other risk factors such as age, gender, urbanization, occupation, and comorbidity. In addition, interactions of comorbidities including infections, preterm low birth weight, and other fetal and newborn respiratory conditions were associated with a higher risk of allergic rhinitis in patients with neonatal UTI than in those without UTI.

The hygiene hypothesis, proposed by Strachan, states that the risk of developing allergies and asthma is inversely related to infection;[6,13] however, the results obtained by Montgomery et al were not consistent with the hygiene hypothesis.

Montgomery et al[14] found that newborns spent their first night in a worse hygiene communal nursery were at an increased risk of developing hay fever. The findings suppose that the dysfunction of immune system development is strongly related to early exposure to infectious agents. However, the other findings reported by McKeever et al[9] do not support the hygiene hypothesis. The study of McKeever et al demonstrated a sufficient statistical power to survey the effects for 14 types of infections within the first 6-months after; however, UTI was not included in the 14 types of infections. The study of McKeever et al showed that none of these infections could protect from developing of allergic diseases persistently. In addition, these authors could not find the confirmatory evidence to suggest that antibiotics would have increased risk to develop allergic diseases. In the other large population-based study, Algert et al[15] found that the exposure to UTI in utero caused an increased risk of childhood asthma, which support that immune system response is the related risk factor rather than the specific organism.

Some studies found poor innate immune factors would induce infections from *Escherichia coli*, *Streptococcus pneumoniae*, *Salmonella enteritidis*, and rhinovirus.[15,16] The possible mechanism is that allergic sensitization would induce similar poor innate immunity by toll-like receptor (TLR) transduction and loss-of-function TLR mutations, which may associate with the risk to develop asthma.[17] The possible effects about innate immune responses to develop allergy are related to the dose, timing, and stimulation site.[18] Repeated administration of the high-dose TLR agonist in the airways would induce the response of T-helper cell 1 (Th1) on the allergen exposure. However, the exposure from low-dose TLR agonists would be related to the immune response about T-helper cell 2 (Th2).[19,20]

Furthermore, natural helper cells could produce a high level of interleukin (IL)-5 and IL-13, which would induce the hyperplasia of eosinophilia or goblet cell that could play an important role for Th2-response.[21] Thereby, these microorganisms would damage the innate immune system, then impaired Th1, but activated Th2-response. Therefore, it could induce the sensitization reaction to allergic rhinitis, which might explain why neonatal UTI could be a risk factor to develop allergic rhinitis.

The strength of the present study is the precise analysis of the future risk of allergic rhinitis in children with neonatal UTI based on a large population database with minimal selection bias. Although the differences between the UTI and non-UTI cohorts in other infections, jaundice, and preterm births were

TABLE 3. The Adjusted Hazard Ratios of Allergic Rhinitis Associated Urinary Tract Infection (UTI) Interaction With Gender or Comorbidity

	Variable	N	Event	Adjusted HR (95% CI)	*P*-Value[†]
UTI	Gender				0.8636
−	Girls	5566	1786	Ref[‡]	
−	Boys	7562	2918	1.27 (1.20–1.34)***	
+	Girls	1392	574	1.32 (1.20–1.47)***	
+	Boys	1893	921	1.67 (1.53–1.82)***	
UTI	Comorbidity				0.0017
−	−	11, 880	4176	Ref[§]	
−	+	1248	528	1.25 (1.14–1.37)***	
+	−	1326	589	1.43 (1.30–1.55)***	
+	+	1959	906	1.45 (1.35–1.56)***	
UTI	Infections				0.0380
−	−	12,765	4547	Ref[‖]	
−	+	363	157	1.29 (1.10–1.52)**	
+	−	2065	921	1.39 (1.29–1.49)***	
+	+	1220	574	1.47 (1.35–1.61)***	
UTI	Neonatal jaundice				0.0782
−	−	12,337	4375	Ref[‖]	
−	+	791	329	1.18 (1.06–1.32)**	
+	−	2075	920	1.40 (1.30–1.50)***	
+	+	1210	575	1.47 (1.35–1.61)***	
UTI	Preterm low birth weight				0.0085
−	−	12,745	4561	Ref[‖]	
−	+	383	143	1.09 (0.92–1.29)	
+	−	3108	1434	1.43 (1.35–1.52)***	
+	+	177	61	1.04 (0.81–1.34)	
UTI	Other fetal and newborn respiratory conditions				0.0420
−	−	12,825	4576	Ref[‖]	
−	+	303	128	1.30 (1.09–1.54)**	
+	−	3153	1440	1.42 (1.34–1.51)***	
+	+	132	55	1.33 (1.02–1.74)*	

CI = confidence interval, HR = hazard ratio, ref = reference group, the reference group was the lowest risk of allergic rhinitis, UTI = urinary tract infection.

[‡] Model adjusted for age, urbanization, occupation and history of comorbidity.

[§] Model adjusted for age, gender, urbanization and occupation.

[‖] Model manual adjusted for age, gender, urbanization, occupation and comorbidities of infections, neonatal jaundice, preterm low birth weight, and other fetal and newborn respiratory conditions.

[†] *P*-value for the interaction.

* $P < 0.05$

** $P < 0.01$.

*** $P < 0.001$.

significant, we corrected for these comorbidities and observed that the UTI cohort still had a higher risk of allergic rhinitis than that of the non-UTI cohort even after propensity score matching. In other words, the results strongly evidence that neonatal UTI is related to allergic rhinitis.

However, limitations of our study must be mentioned. First, the diagnoses of UTI and allergic rhinitis were based on ICD-9-CM codes, and urine culture, blood sampling for genotyping, and examination of the immunoglobulin E level, IL-13, or TLR polymorphisms were not performed. The NHIRD covers a highly representative sample of Taiwan's general population because the reimbursement policy is universal and operated by a single buyer, the Taiwan government. All insurance claims are scrutinized by medical reimbursement specialists and subjected to peer review according to standard diagnosis criteria. If specialists or physicians misdiagnosed diseases or miscoded diagnoses, they would be subject to the punitive action. Therefore, the diagnoses of UTI and allergic rhinitis in this study were highly reliable.

Second, family history of atopy was unavailable in this study. This crucial risk factor may be related to the different prevalence of the familial predisposition to atopy in the 2 study cohorts. Third, the period of study was only 6 years; a longer follow-up duration should be examined. Fourth, antibiotic treatment can influence the development of common allergic disease in later childhood.[22] However, we could not determine whether antibiotics are another risk factor for subsequent allergic rhinitis because it was impossible to enroll newborns with UTI who did not receive antibiotic treatment in our study. Therefore, determining confounding factors associated with antibiotics or UTI may require a meticulously designed study that compares the allergic rhinitis incidence between UTI patients with antibiotics and those without antibiotics.

CONCLUSION

We found an association between neonatal UTI with subsequent developing allergic rhinitis in this retrospective population-based cohort study. Although our study design had included adequate control of possible confounding factors and biases, there is still lack of some unmeasured or unknown confounding factors. In addition, the level of evidence of a retrospective cohort study is lower than a prospective cohort or randomized-controlled study. Therefore, further well-designed studies are necessary to evaluate the effects of neonatal UTI for developing the immune system and the pathophysiology of allergic rhinitis.

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