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ARTICLE

The Association with rhegmatogenous retinal detachment and paediatric atopic dermatitis: a 12-year Nationwide Cohort Study

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Abstract

Purpose Historically, atopic dermatitis (AD) is associated with an increased risk of rhegmatogenous retinal detachment (RRD). However, uncertainty remained regarding the effect of AD itself and comorbidities (e.g., allergic diseases, cataract surgery) on RRD occurrence in a large, population-based paediatric population.

Patients and methods We analysed the 12-year National Health Insurance Service database (2002–2013) covering the entire Korean population to estimate the association between AD and RRD in people aged under 20 years.

Results We identified 3142 RRD patients, and matched 18,852 controls (six controls to each RRD patient); therefore, we included 21,994 peoples under aged 20 years in the analyses. AD was more prevalent in the RRD group (329 patients, 10.47%) than the control group (1043 patients, 5.53%; $P < 0.001$), and so were severe AD (153 patients [4.87%] and 223 patients [1.18%], respectively; $P < 0.001$). In conditional logistic regression analysis, AD was associated with RRD (OR, 1.61; 95% CI, 1.93–1.87) even after adjusting for allergic conditions, connective tissue disease, uveitis, and cataract surgery. In addition, severity of AD was associated with an increased risk of RRD (OR for non-severe AD and severe AD, 1.26 [95% CI, 1.05–1.51] and 2.88 [95% CI, 2.25–3.68]).

Conclusion This study suggests that AD itself is a risk factor of RRD in children by showing the association between AD and RRD occurrence and the biologic gradient even after adjustment for known confounders including allergic conditions, uveitis, and cataract surgery.

Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disease of childhood, affecting between 10% and 20% of children in industrialised countries [1–3]. Patients with AD are frequently predisposed to ocular complications, such as blepharitis, keratoconjunctivitis, keratoconus, cataract, and rhegmatogenous retinal detachment (RRD) [1, 4, 5]. Of these, RRD is the most serious complication; it can lead to the loss of vision [6], which could be a great obstacle in life for young patients. Historically, AD has been considered to be causally involved in the development of RRD. However, evidence regarding the association between AD and RRD occurrence has been derived from case reports and small observation studies. [4, 7–11] Postulated mechanisms of RRD in those with AD include trauma such as rubbing eyes repeatedly for relieving itching, which affects the occurrence of RRD. [4, 7–11] In addition, one of the other ophthalmic complications of AD is cataract, and it is reported that cataract surgery itself can cause RRD [5, 12]. Therefore, it is important to analyse the association between AD and RRD occurrence in conjunction with several comorbidities. We aimed to describe the association between AD and RRD occurrence using a 12-year, population-based database covering the entire Korean population.

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Subjects and methods

We conducted a retrospective cohort study using data from the National Health Insurance Service (NHIS) database from 2002 to 2013. The NHIS database includes records for the entire Korean population, since the government-led single payer programme covers the entire Korean population, about 50 million persons, through either the National Health Insurance system (97%) or medical aid (3%) [13]. Therefore, the NHIS database contains all medical records related to medical claims made in Korea. We analysed two different NHIS datasets simultaneously in the present study: (1) the NHIS-customised database, which consists of patients with RRD extracted from the whole NHIS database covering the entire Korean population, and (2) the NHIS-National Sample Cohort (NSC) database, which consists of a validated and representative sample of 1,025,340 Korean residents (~2.2% of Korean population) [14]. As the NHIS did not allow us to access the whole database to set the non-RRD population, we used the NHIS-NSC database instead to set the control population. Detailed information regarding the Korean national claims database has been reported elsewhere [15–20]. This study was approved by the institutional review board (IRB) of Seoul National University Bundang Hospital (IRB No.X-1606–352–901), and complied with the guidelines of the Declaration of Helsinki.

We identified all cases of incident RRD using the diagnostic code H33.0, in accordance with the International Classification of Diseases, 10th edition. For strict definition of RRD, we only included cases of surgical RRD which were simultaneously claimed under relevant diagnostic and surgical codes. The surgical codes for RRD are S5130 (scleral buckling surgery), S5121 (vitrectomy, total), and S5122 (vitrectomy, partial). Index date was defined as the date of earliest claim with an RRD diagnostic code. To identify cases of incident RRD, we excluded cases with RRD diagnostic codes during the first 2 years of the study period (i.e., 2002 and 2003). Among patients with incident RRD, we only included those below the age of 20 years on the index date. A total of 3142 patients diagnosed with RRD between 2004 and 2013 met the eligibility criteria.

Then, we selected six control subjects for each patient in the RRD group by propensity-based matching after stratification of the overall cohort according to the year of index date. Propensity scores were estimated by multiple logistic regression analysis in each year for all beneficiaries throughout the study period, without regard to outcomes. A model was developed that included age, sex, residential area, and household income in every study year as covariables.

Among these patients and matched control subjects, we identified patients with AD when they had at least one claim with the AD diagnostic code (L20) within 2 years before the index date. In addition, among these patients with AD, we also identified those with severe AD on the basis of their usage of prescribed drugs recommended for moderate to severe AD in the guidelines for AD treatment [21–24]. We assigned patients with AD to the severe AD group when they had received any prior therapy including (1) one or more treatments of omalizumab, intravenous immunoglobulin, interferon gamma, or rituximab and/or (2) two or more weeks of treatment with cyclosporine, azathioprine, mycophenolate mofetil, methotrexate, or steroids within 2 years before the index date.

Then, we defined history of asthma (J45.0 and J45.9) and allergic rhinitis (J30.1, J30.2, J30.3, and J30.4) when individuals had at least one claim with the diagnostic code for each of these diseases within 2 years before the index date. In addition, we identified history of cataract surgery, connective tissue disease, and uveitis as potential confounders. We defined the history of cataract surgery when patients had (1) the treatment code (S5111, S5119, S5112 and S5110) related to cataract surgery before the index date or (2) the diagnostic code (Z96.1) related to the presence of the intraocular lens before the index date. Connective tissue diseases (CTD) (inflammatory polyarthropathies [M05-M14] systemic connective tissue disorders [M30-M36]) and uveitis (iridocyclitis [H20] and chorioretinal inflammation [H30]) were identified using the diagnostic codes within 2 years before the index date.

Statistical analysis

Statistical analyses were performed using SAS (version 9.2; SAS Institute, Inc., Cary, NC). For descriptive analysis, we used the Chi-square test and t test for comparison of general characteristics of subjects. We applied conditional logistic analysis to assess the association between AD and RRD occurrence by the use of odds ratio (OR) and 95% confidence interval (CI). We set the presence of AD as an independent variable in Models A, and B, we used the severity of AD (no AD, non-severe AD, and severe AD) as an independent variable. We performed the univariable analysis, multivariable analysis 1 adjusting for history of asthma and allergic rhinitis, and multivariable analysis 2 adjusting for history of asthma, allergic rhinitis, cataract surgery, CTD, and uveitis in both Models A and B. In addition, we performed sensitivity analyses after stratification according to potential confounders (cataract surgery, uveitis, allergic rhinitis and asthma). Statistical significance was set at $P < 0.05$.

Results

We included 3142 patients with RRD and 18,852 matched-controls in the analysis (Fig. 1). As shown in Table 1, the
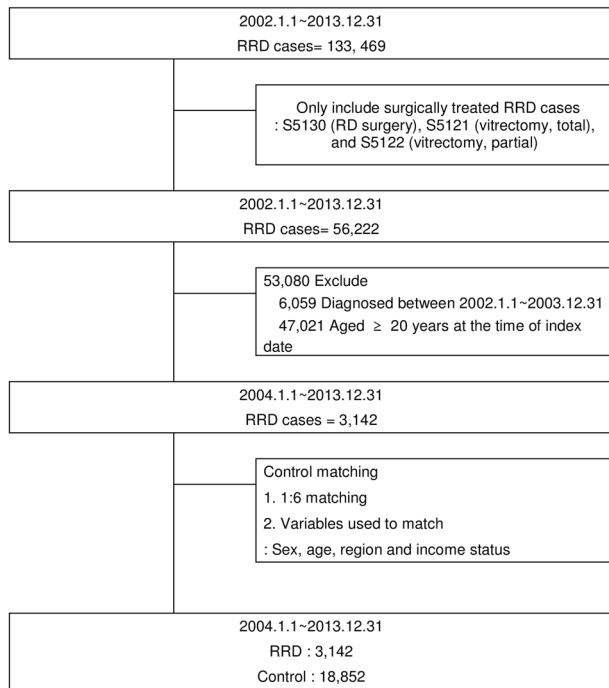
Fig. 1 Flow chart regarding the selection of pediatric patients having rhegmatogenous retinal detachment (RRD) and their 1:6 matched controls according to the eligible criteria.

RRD group and their matched-controls had similar characteristics in age, sex, residential regions, and household income. AD was more prevalent in the RRD group (329 patients, 10.47%) compared to the control group (1,043 patients, 5.53%; $P < 0.001$), and among these, the severe AD was also more prevalent than the control group (153 patients, 4.87% and 223 patients, 1.18%, respectively; $P < 0.001$). Other comorbidities (asthma, allergic rhinitis, CTD, cataract surgery, and uveitis) were also more prevalent in the RRD group compared to the control group.

Table 2 presents the results of the conditional logistic regression analyses in the Models A and B. Briefly, in the Model A, AD was associated with RRD even in the multivariate analyses 1 (OR, 1.94; 95% CI, 1.70–2.21) and 2 (OR, 1.61; 95% CI, 1.39–1.87). The Model B shows similar results; the non-severe AD and the severe AD were associated with RRD with a biological gradient; the effect of the severe AD was significantly higher than that of the non-severe AD (OR of the non-severe AD was 1.33 [95% CI, 1.12–1.57] and 1.26 [95% CI, 1.05–1.51] in multivariable analysis 1 and 2, respectively and that of the severe AD was 4.18 [95% CI, 3.37–5.17] and 2.88 [95% CI, 2.25–3.68] in multivariable analyses 1 and 2, respectively). Allergic rhinitis, cataract surgery, CTD, and uveitis were also associated with RRD in both the Models A and B. The sensitivity analyses showed consistent and robust associations between RRD and AD even after the stratification and even after excluding the cataract surgery, uveitis, allergic

Table 1 Comparison of baseline characteristics between the RRD and control groups.

	RRD group		Control Group		P value*
	No.	%	No.	%	
Total	3142		18852		
Age					1.000
0	10	0.32	60	0.32	
1–4	14	0.45	84	0.45	
5–9	126	4.01	756	4.01	
10–14	778	24.76	4668	24.76	
15–19	2214	70.46	13284	70.46	
Sex					1.000
Male	2316	73.71	13896	73.71	
Female	826	26.29	4956	26.29	
Residential region					1.000
Seoul/Incheon	808	25.72	4843	25.69	
Gyeonggi/Gangwon	804	25.59	4824	25.59	
Busan/Daegu/Ulsan/Gyeongsang	914	29.09	5488	29.11	
Daejeon/Sejong/Chungcheong	298	9.48	1788	9.48	
Gwangju/Jeolla/Jeju	318	10.12	1909	10.13	
Household income					1.000
Low	1111	35.36	6666	35.36	
Middle	1003	31.92	6018	31.92	
High	1028	32.72	6168	32.72	
Atopic dermatitis					
Atopic dermatitis	329	10.47	1043	5.53	**<0.0001**
Severe atopic dermatitis	153	4.87	223	1.18	**<0.0001**
Comorbidity					
Asthma	855	27.21	4545	24.11	**0.0002**
Allergic rhinitis	1349	42.93	6615	35.09	**<0.0001**
Connective tissue disease	85	2.71	276	1.46	**<0.0001**
Cataract surgery	152	4.84	4	0.02	**<0.0001**
Uveitis	185	5.89	36	0.19	**<0.0001**

RRD rhegmatogenous retinal detachment.

*Chi-square test. Bold-face values indicate $P < 0.05$.

rhinitis and asthma from the analysis (Supplementary Materials).

Discussion

AD, a common condition in childhood, is associated with an increased risk of RRD occurrence, a challenging disease in children. To the best of our knowledge, this study is the first nationwide population-based study assessing the association between AD and RRD. AD may be important for preventing serious complications such as RRD.

The incidence of RRD in the paediatric population—accounting for 3–12% of all RRD cases—is lower than that in adults [6, 25]. AD is well known as an important risk factor for paediatric RRD, especially in Japan [10, 11, 26–28]. The incidence of RRD in patients with AD had been reported to be 0.5–11%, with an especially higher rate in Japan than in

Table 2 Association between rhegmatogenous retinal detachment and AD.

	Univariable analysis		Multivariable analysis 1			Multivariable analysis 2		
	OR (95% CI)	*p* value		OR (95% CI)	*p* value		OR (95% CI)	*p* value
Model A								
AD	2.02 (1.77–2.31)	**<0.0001***	**AD**	1.94 (1.70–2.21)	**<0.0001***	**AD**	1.61 (1.39–1.87)	**<0.0001***
			Asthma	0.90 (0.81–1.02)	0.0872	**Asthma**	0.90 (0.79–1.01)	0.0726
			Allergic rhinitis	1.55 (1.40–1.72)	**<0.0001***	**Allergic rhinitis**	1.55 (1.39–1.73)	**<0.0001***
						Cataract surgery	176.5 (65.04–479.25)	**<0.0001***
						Connective tissue disease	1.74 (1.34–2.26)	**<0.0001***
						Uveitis	28.61 (19.57–41.84)	**<0.0001***
Model B								
AD			**AD**			**AD**		
No AD	1 (reference)		No AD	1 (reference)		No AD	1 (reference)	
Non-severe AD	1.37 (1.16–1.62)	**<0.0001***	non-severe AD	1.33 (1.12–1.57)	**<0.0001***	non-severe AD	1.26 (1.05–1.51)	**0.0061***
Severe AD	4.43 (3.59–5.48)	**<0.0001***	severe AD	4.18 (3.37–5.17)	**<0.0001***	severe AD	2.88 (2.25–3.68)	**<0.0001***
			Asthma	0.90 (0.80–1.01)	0.0826	**Asthma**	0.90 (0.79–1.01)	0.0732
			Allergic rhinitis	1.54 (1.39–1.71)	**<0.0001***	**Allergic rhinitis**	1.54 (1.38–1.72)	**<0.0001***
						Cataract surgery	163.6 (60.29–444.07)	**<0.0001***
						Connective tissue disease	1.74 (1.34–2.26)	**<0.0001***
						Uveitis	28.28 (19.31–41.41)	**<0.0001***

AD atopic dermatitis, *AR* allergic rhinitis, *OR* odds ratio, *CI* confidence interval.

*$P < 0.05$.

Western countries [6, 11, 26, 29, 30]. The proportion of patients with AD in the paediatric population with RRD was 3–18%. [7, 30–32] In the present study, the proportion of patients with AD in the paediatric with RRD was 10.47%, which is similar to those reported in previous studies. In terms of sex distribution, the male ratio was higher in the RRD group, regardless of whether or not they were accompanied by AD (Table 3). In a previous study, despite a similarity in sex distribution among patients with AD, the male-to-female ratio among patients with RRD with AD was reported to be 1.5–2:1 [10, 11]. However, it is difficult to determine whether sex affects the relationship between RRD and AD, because the general incidence of RRD has been reported to be higher among men than among women, especially in the younger age group [25].

AD is often the first presenting condition of the atopic march, a typical progression of allergic diseases including allergic rhinitis and asthma [1, 33]. Many epidemiologic studies have shown that AD is associated with asthma and allergic rhinitis [1, 33]. Therefore, we carefully adjusted these allergic conditions in the analyses.

Dermatologists use the indexes, e.g., the SCORing Atopic Dermatitis (SCORAD) index, Eczema Area and Severity Index (EASI), or Investigator's Global Assessment (IGA) index, to determine the AD severity in their clinics, which are based on physician's estimates of disease extent (SCORAD, EASI, and IGA) and subjective patient's assessment of itching and sleep loss (SCORAD) [21, 34]. However, it is impossible to access these severity data for each AD patient in the insurance database. Therefore, we

defined the severe AD on the basis of usage of prescription drugs which are recommended for moderate to severe AD in the widely accepted guidelines for AD treatment [22, 23, 35]. Using this definition for severe AD, we found a biological gradient in the effect of AD severity on RRD occurrence, which implies the causal relationship between AD and RRD.

The association between AD and RRD occurrence was statistically significant even after adjusting for possible confounders such as allergic diseases, CTD, uveitis, and history of cataract surgery in our study. Among these, evidence suggests that cataract surgery is causally involved in RRD occurrence in children; in recent study, a 5.5% risk for RRD is estimated within first 10 years after cataract surgery in childhood [12, 36]. It is also known that cataract is one of the various complications of uveitis [37, 38]. In addition, CTD is frequently accompanied by uveitis, and cataract may be caused by steroids, which are mainly used for the treatment of CTD [39]. Therefore, in this study, we analysed the relationship between uveitis and CTD and RRD. This study reveals a framework for understanding the effects of these conditions on RRD. As in literature, the effect of cataract surgery on RRD occurrence was very high in the present study (OR = 176.5) and that of uveitis was also quite high (OR = 28.28). The effect of allergic rhinitis and CTD were also statistically significantly high, while asthma was not. As stated, even after adjusting for these conditions, AD was associated with RRD in our study.

Although there have been many reports of a relatively high incidence of RRD among patients with AD, there has

Table 3 Comparison of baseline characteristics between patients with RRD with and without AD.

	RRD with AD		RRD without AD		P value*
	No.	%	No.	%	
Total	329	10.47	2,813	89.53	
Age					0.1791
0	0	0.00	10	0.36	
1–4	3	0.91	11	0.39	
5–9	19	5.78	107	3.80	
10–14	84	25.53	694	24.67	
15–19	223	67.78	1991	70.78	
Sex					**<0.0001**
Male	211	64.13	2105	74.83	
Female	118	35.87	708	25.17	
Residential region					0.4493
Seoul/Incheon	77	23.40	731	25.99	
Gyeonggi/Gangwon	90	27.36	714	25.38	
Busan/Daegu/Ulsan/Gyeongsang	88	26.75	826	29.36	
Daejeon/Sejong/Chungcheong	34	10.33	264	9.38	
Gwangju/Jeolla/Jeju	40	12.16	278	9.88	
Household income					0.2977
Low	108	32.83	1003	35.66	
Middle	101	30.70	902	32.07	
High	120	36.47	908	32.28	
Comorbidity					
Asthma	130	39.51	725	25.77	**<0.0001**
Allergic rhinitis	183	55.62	1166	41.45	**<0.0001**
Connective tissue disease	9	2.74	76	2.7	0.9715
Cataract surgery	57	17.33	95	3.38	**<0.0001**
Uveitis	38	11.55	147	5.23	**<0.0001**

AD atopic dermatitis, *RRD* rhegmatogenous retinal detachment.

*Chi-square test. Bold-face values indicate $P < 0.05$.

been no large-scale study to determine whether the risk of RRD increases with the severity of AD. In a previous study involving 79 patients with severe AD, serum immunoglobulin E levels, history of other allergic diseases (asthma and allergic rhinitis), and treatment with systemic corticosteroids were not associated with occurrence of RRD [31]. However, a recent study in Japan reported a statistically significant decrease in the number of patients with RRD with AD after the 2000s [28]. These changes might be associated with advances in AD therapy, including the development of new therapeutic tools, which suggests that active treatment of AD is important for preventing the development of AD-associated RRD [28]. On the basis of these results, it can be inferred that severity of AD might be related to the occurrence of RRD. This finding is meaningful in that this is the first study to confirm this result by analysis of large-scale, nationwide data.

The pathogenesis of RRD in patients with AD has not yet been elucidated. Many reports have postulated that repetitive trauma near the eyes is the main causative factor of RRD in AD [8, 10, 40]. The most characteristic symptom of AD is severe itching, which often involves the face [1, 21]. Patients with AD often habitually rub or slap the periorbital area in order to relieve itching, and this repetitive trauma might be associated with the development of RRD [7, 10, 26]. This hypothesis is supported by reports that the fundus findings of AD-associated RRD are similar to those of traumatic RRD [7, 8, 10]. In addition, the fact that both the retina and skin are of embryonic neuroectodermal origin suggests that AD causes not only cutaneous inflammation but also intraocular inflammation leading to RRD [10, 41]. For this reason, it is suggested that tissue degeneration and tearing are caused by chronic inflammation of the vitreous base, peripheral retina, and ciliary body in AD [9, 10, 42]. Thus, RRD in AD is thought to be caused by various pathogenic mechanisms, and more research is required on the basis of ophthalmologic findings in a greater number of patients.

The present study has certain strengths relative to previous studies. We used a long-term nationwide population-based database covering the entire Korean population to identify the association between AD and RRD. To the best of our knowledge, this is the largest study ever. In addition, this study is the first to reveal the impact of severity of AD on the risk of RRD and the effects of comorbidities on RRD occurrence.

Despite these strengths, this study suffers from the following limitations. First, we might have underestimated the incidence of RRD in the cohort. For diagnostic accuracy, we only included patients with RRD who had received surgical treatment, such as scleral buckling or vitrectomy. There are other options for treatment of RRD, such as laser therapy, cryopexy, and pneumopexy; therefore, the incidence of RRD might have been underestimated [6]. Alternately, the incidence of AD is likely to have been overestimated because it was calculated solely on the basis of diagnostic code, which might be less accurate than diagnosis on the basis of hospital-based medical records and clinical data. In addition, the effect of myopia on the development of RRD can be considered, but it was impossible to confirm the degree of refractive error due to the nature of this study based on the claim database. However, since the association between AD and myopia is rarely known, the lack of inclusion of myopia in the analysis would not have a significant impact on the outcome of this study. For similar reasons, we could not consider factors such as anatomical distribution of AD, genetic/environmental data, and other factors that have been reported to be associated with RRD in AD. Considering

previous studies that reported higher rates in Japan than in Western countries, there is also a possibility of racial differences among the Korean population [9–11, 26, 29]. In addition, although we employed a large cohort sample, the sample size of the RRD group was relatively small, because the incidence of RRD was rare among subjects below the age of 20 years.

In conclusion, this study presents the biologic gradient in association between AD and RRD even after adjusting possible comorbidities including allergic diseases, uveitis, and surgical procedures for cataract, which suggests that AD itself might be a risk factor of RRD in paediatric population. Relative to RRD of other aetiologies, AD-associated RRD has worse surgical outcomes and higher frequency of recurrence [27, 30]. If AD is not well controlled after surgery for RRD, prolonged trauma—such as that from eye rubbing and slapping—might persist, leading to poor prognosis. Therefore, active treatment of AD is very important for preventing not only skin disease but also other serious complications such as RRD. In severe AD, especially, careful ophthalmic examination is needed not only during treatment but also during the follow-up period.

Summary

What was known before

- Patients with atopic dermatitis are frequently predisposed to ocular complications.

What this study adds

- Atopic dermatitis itself might be a risk factor of rhegmatogenous retinal detachment in paediatric population.
- Active treatment of atopic dermatitis is important for preventing serious complications such as rhegmatogenous retinal detachment.

Compliance with ethical standards

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