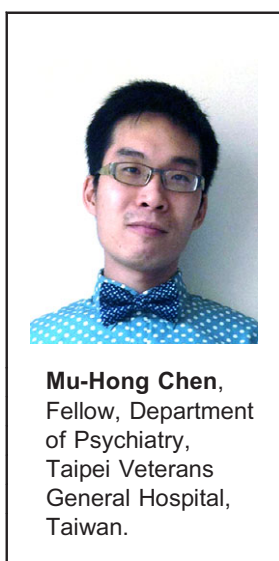




Risk of epilepsy among patients with atopic dermatitis: A nationwide longitudinal study

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Epilepsia, **(*)1–6, 2014
doi: 10.1111/epi.12667



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SUMMARY

Objective: Both atopic dermatitis and epilepsy have been regarded as chronic inflammatory diseases. However, their association has yet to be investigated.

Methods: Using the Taiwan National Health Insurance Research Database, 35,312 patients with atopic dermatitis but without a history of epilepsy, and 35,312 age-/gender-matched controls were enrolled between 1998 and 2008, and followed to the end of 2011 to identify the development of epilepsy.

Results: Subjects with atopic dermatitis had a higher incidence of developing epilepsy (0.94 vs. 0.27/1,000 person-years, $p < 0.001$) than the control group. The Cox regression model showed that atopic dermatitis increased the risk of developing epilepsy (hazard ratio [HR] 2.91, 95% confidence interval [CI] 2.23–3.82) after adjusting for demographic data and medical comorbidities. Sensitivity tests showed consistent findings (HR 2.32, 95% CI 1.68–2.96) after excluding the first year of observation. In addition, asthma (HR 1.34, 95% CI 1.04–1.72) and allergic rhinitis (HR 1.34, 95% CI 1.04–1.73) were related to the risk of epilepsy.

Significance: Subjects with atopic dermatitis were associated with an increased risk of developing epilepsy in later life. Further studies would be needed to investigate the underlying mechanisms.

KEY WORDS: Atopic dermatitis, Epilepsy, Comorbidities.

Epilepsy is one of the most common neurologic diseases in the world. It affects approximately 2 million people in the United States and >50 million people worldwide, with 16–51 cases of new-onset epilepsy per 100,000 people every year.^{1–3} The majority of adults with epilepsy experience a childhood onset; >300,000 children aged between 5 and 14 years have active epilepsy in the United States.⁴ Epilepsy not only affects people with epilepsy, due to the

concomitant physical hazards and the unpredictability of epileptic attacks, but also is a burden on the family and society-at-large, including the disability of epilepsy-related work/academic loss and the health care costs.^{5–7} Nearly one fourth of patients with epilepsy are medication resistant, and the definite pathophysiology of epilepsy is still unclear.^{1–3}

Previous studies have suggested the importance of neuro-inflammation and related cytokines in epilepsy and epileptogenesis, and these possible contributing factors have gained more scientific and clinical attention in recent years. Mao et al.⁸ analyzed cytokine levels in 70 patients with epilepsy and 68 healthy controls, and reported that a positive correlation was noted between interleukin (IL)-17 α , IL-6 levels, and the Veterans Administration Seizures Frequency and Severity Rating Scale score, and between interferon (IFN)- γ , IL-10, levels, and the National Hospital Seizure Severity Scale score. These authors further suggested the level of IL-17 α was significantly correlated with seizure

Accepted April 22, 2014.

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frequency.⁸ Tiwari et al.⁹ reported that the IL-6-174G>C (rs1800795) polymorphism had a significant association with the frequency of epileptic attacks and drug-refractory epilepsy. The interactions among the glia, immune cells, and neurons contribute to the initiation, propagation, and vicious cycle of neuroinflammation, although the glia-immune cell connection remains to be clarified.^{10–12} Other evidence indicated the important roles of microglial cells and mast cells and their interaction in neuroinflammation.^{13,14}

The association between atopic dermatitis and epilepsy is still unknown. Some evidence indicates that atopic dermatitis is a chronic systemic inflammatory disease in which mast cells play a crucial role in both acute and chronic atopic responses following exposure to allergens.^{15,16} A case report described a de novo deletion of chromosome 22q13.2, containing the *SHANK3*, *NCAPH2*, and *CYP2D6* genes, which are associated with the T-cell immune response in this region, in a 5-year-old boy with autistic features, epilepsy, developmental delay, and atopic dermatitis.¹⁷ This finding may hint a possible relationship, or even a shared genetic pathophysiology, between atopic dermatitis and epilepsy. The concept of a brain-skin connection was also suggested in previous reports, and that atopic dermatitis increased the risk of other neuropsychiatric disorders.^{18–20} However, there has been no study investigating the potential role of atopic dermatitis in epilepsy.

Using the Taiwan National Health Insurance Research Database (NHIRD) with a large sample-size and a longitudinal follow-up study design, we attempted to investigate the temporal association between atopic dermatitis and epilepsy. We hypothesized that atopic dermatitis increased the risk of developing epilepsy in later life.

METHODS

Data source

Taiwan's National Health Insurance (NHI), a mandatory universal health insurance program, was implemented in 1995 and offers comprehensive medical care coverage to all Taiwanese residents. The National Health Research Institute (NHRI) is in charge of the entire insurance claims database, namely the National Health Insurance Research Database (NHIRD), which consists of health care data from >97% of the entire Taiwan population (<http://nhird.nhri.org.tw/>). The NHRI audits and releases the NHIRD for scientific and study purposes. To maintain individual privacy, claims data of subjects included in the NHIRD are anonymous. Comprehensive information on insured subjects is included in the database, including demographic data, dates of clinical visits, and disease diagnoses. The diagnostic codes used were based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). The NHIRD has been used extensively in many epidemiologic studies in Taiwan.^{21,22}

Inclusion criteria for subjects with atopic dermatitis and the control group

For the study, 1,000,000 subjects, approximately 4.3% of the population of Taiwan, were randomly selected from the NHIRD. Subjects who were identified as having newly diagnosed atopic dermatitis (ICD-9-CM codes: 691 or 691.8) diagnosed by dermatologists or pediatricians between January 1, 1998 and December 31, 2008, and who had no history of epilepsy (ICD-9-CM code: 345) before enrollment, were included as the atopic dermatitis cohort. The time of the diagnosis of atopic dermatitis was regarded as the time of enrollment. The age- and gender-matched (1:1) control cohort was identified randomly from among the 1,000,000 subjects after eliminating the study subjects, those who had been given a diagnosis of atopic dermatitis at any time, and those with epilepsy before enrollment. Diagnoses of epilepsy (ICD-9-CM code: 345) given by neurologists or pediatricians were identified during the follow-up (from enrollment to December 31, 2011, or to death). Due to the high comorbidity of other allergic diseases with atopic dermatitis, we assessed the comorbid effects of different allergic diseases in the risk of developing epilepsy. Allergic rhinitis (ICD-9-CM code: 477) diagnosed by internists, pulmonologists, rheumatologists, otolaryngologists, or pediatricians; asthma (ICD-9-CM codes: 493) diagnosed by pulmonologists, rheumatologists, or pediatricians; and allergic conjunctivitis (ICD-9-CM codes: 372.05, 372.10, and 372.14) diagnosed by ophthalmologists were identified. In addition, other epilepsy-related risk factors were also assessed, including cerebrovascular diseases (ICD-9-CM codes: 430–438) diagnosed by emergency room doctors, neurologists, neurosurgeons, or pediatricians; meningitis and encephalitis (ICD-9-CM codes: 320, 321, 322, 323, 324.0, 325) diagnosed by neurologists, infection specialists, and pediatricians; and head injury (ICD-9-CM codes: 800–804, 850–854, or 959) diagnosed by emergency room doctors, neurologists, neurosurgeons, or pediatricians. All diagnoses were given at least twice by corresponding physicians to achieve diagnostic validity. Level of urbanization (level 1 to level 5; level 1, most urbanized region; level 5, least urbanized region) was also assessed for our study. This study was approved by the of Taipei Veterans General Hospital, Taiwan Institutional Review Board.

Statistical analysis

For between-group comparisons, the independent *t*-test was used for continuous variables and Pearson's chi-square test for nominal variables, where appropriate. The Cox regression model was used to investigate the hazard ratio (HR) with a 95% confidence interval (CI) of epilepsy between subjects with atopic dermatitis and control group after adjusting for demographic data and medical comorbidities. Sensitivity analyses were performed to investigate the associations discussed earlier after excluding the first year of observation. We also performed subanalysis of the risk of

epilepsy with atopic dermatitis stratified by age group: children (<18 years), adults (18–64 years), and the elderly (≥ 65 years). A two-tailed p -value of <0.05 was considered statistically significant. All data processing and statistical analyses were performed with Statistical Package for Social Science (SPSS) version 17 software (SPSS Inc., Chicago, IL, U.S.A.) and Statistical Analysis Software (SAS) version 9.1 (SAS Institute, Cary, NC, U.S.A.).

RESULTS

In all, 35,312 patients with atopic dermatitis and 35,312 age-/gender-matched controls were enrolled in our study, with an average follow-up of 7.63 ± 2.88 years. The atopic dermatitis cohort exhibited an increased incidence of epilepsy (0.94 vs. 0.27 1,000 person-years, $p < 0.001$) and an earlier age at onset of epilepsy (11.27 ± 16.85 vs. 17.57 ± 20.84 years, $p = 0.008$) than the control cohort (Table 1). Patients with atopic dermatitis had a higher prevalence of asthma (29.5% vs. 12.8%, $p < 0.001$), allergic rhinitis (51.2% vs. 28.0%, $p < 0.001$), allergic conjunctivitis (30.8% vs. 18.9%, $p < 0.001$), cerebrovascular diseases (1.6% vs. 1.3%, $p = 0.008$), meningitis and encephalitis (0.3% vs. 0.1%, $p < 0.001$), and head injury (1.9% vs.

1.6%, $p < 0.001$) than the controls (Table 1). Patients with atopic dermatitis resided in more urbanized regions ($p < 0.001$) and had a higher income-related insured amount ($p < 0.001$).

Kaplan-Meier survival analyses with a log-rank test demonstrated that patients with atopic dermatitis had a higher likelihood of developing epilepsy ($p < 0.001$) than the control group (Fig. 1). The Cox regression model showed that atopic dermatitis increased the risk of developing epilepsy (HR 2.91, 95% CI 2.23–3.82) after adjusting for demographic data and medical comorbidities (Table 2). Sensitivity analyses after excluding the first year of observation had consistent findings: atopic dermatitis increased the risk of developing epilepsy (HR 2.32, 95% CI 1.68–2.96).

Subanalysis stratified by age further delineated that only children with atopic dermatitis (HR 3.29, 95% CI 2.44–4.45), and not adults or the elderly, showed a significant relationship between atopic dermatitis and an increased risk of developing epilepsy in later life (Table 2). Comorbid allergic diseases, including asthma (HR 1.34, 95% CI 1.04–1.72) and allergic rhinitis (HR 1.34, 95% CI 1.04–1.73), were related to the increased risk of developing epilepsy (Table 2). In addition, cerebrovascular diseases (HR 11.36, 95% CI 6.09–21.21), meningitis and encephalitis (HR

Table 1. Demographic data of patients with atopic dermatitis and the control group

	Patients with atopic dermatitis (n = 35,312)	Controls (n = 35,312)	p-Value
Age at enrollment (years, SD, n, %)	12.62 (18.40)	12.62 (18.40)	
<18 years	26,026 (73.7)	26,026 (73.7)	
18–64 years	8,430 (23.9)	8,430 (23.9)	
≥ 65 years	856 (2.4)	856 (2.4)	
Gender (M, %)	17,367 (49.2)	17,367 (49.2)	
Epilepsy (n, 1,000 person-years)	253 (0.94)	74 (0.27)	<0.001
Age at diagnosis (years, SD)	11.27 (16.85)	17.57 (20.84)	0.008
Duration between enrollment and diagnosis (years, SD, median, range; n, %)	3.33 (2.72, 2.65, 0–11)	6.22 (2.86, 6.44, 0–11)	<0.001
<1 year	64 (25.3)	1 (1.4)	
1–3 years	73 (28.9)	10 (13.5)	
>3 years	116 (45.8)	63 (85.1)	
Comorbidities (n, %)			
Asthma	10,419 (29.5)	4,523 (12.8)	<0.001
Allergic rhinitis	18,082 (51.2)	9,893 (28.0)	<0.001
Allergic conjunctivitis	10,886 (30.8)	6,680 (18.9)	<0.001
Cerebrovascular disease	576 (1.6)	454 (1.3)	<0.001
Head injury	674 (1.9)	570 (1.6)	0.003
Meningitis and encephalitis	100 (0.3)	51 (0.1)	<0.001
Level of urbanization (n, %)			
1 (most urbanized)	11,817 (33.5)	10,253 (29.0)	<0.001
2	11,042 (31.3)	10,839 (30.7)	
3	5,737 (16.2)	6,320 (17.9)	
4	4,333 (12.3)	4,916 (13.9)	
5 (most rural)	2,383 (6.7)	2,984 (8.5)	
Income-related insured amount			
$\leq 15,840$ NTD/month	28,307 (80.2)	28,074 (79.5)	<0.001
15,841–25,000 NTD/month	3,562 (10.1)	4,076 (11.5)	
$>25,001$ NTD/month	3,443 (9.8)	3,162 (9.0)	

SD, standard deviation; NTD, New Taiwan Dollar.

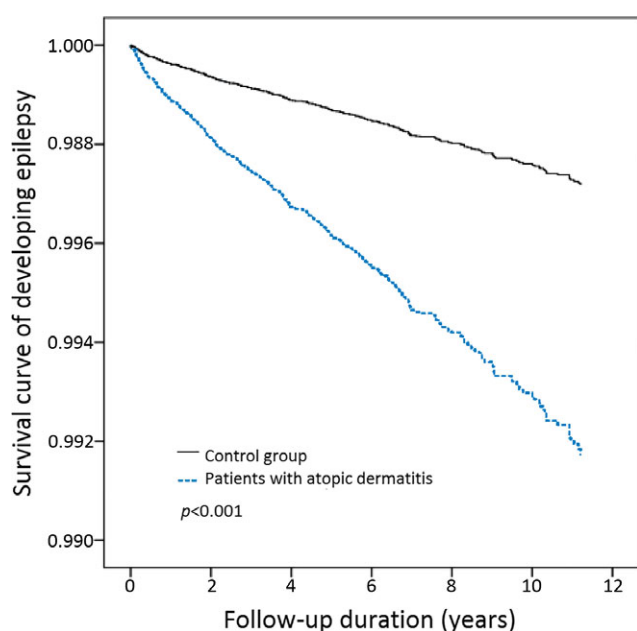


Figure 1.

Survival curve of developing epilepsy among patients with atopic dermatitis and the control group.

Epilepsia © ILAE

13.19, 95% CI 7.64–22.67), and head injury (HR 2.45, 95% CI 1.50–4.02) also increased the risk of developing epilepsy (Table 2).

DISCUSSION

Our results supported the study hypothesis that subjects with atopic dermatitis, especially children, had an increased risk of developing epilepsy in later life. We further found that allergic comorbidities, including asthma and allergic rhinitis, were also related to an increased risk of epilepsy.

Both atopic dermatitis and epilepsy have been regarded as chronic inflammatory diseases. The neuroinflammation and related cytokines in epilepsy and epileptogenesis have garnered clinical and scientific attention in recent

years.^{10–12,23–25} For example, transgenic mice overexpressing tumor necrosis factor (TNF)- α or IL-6 in the brain were predisposed to the occurrence of seizures and neuronal cell loss.²⁶ Overexpression of brain TNF- α and IL-6 in transgenic mice was associated with the occurrence of neurodegenerative changes and sporadic spontaneous seizures.²⁷ Several clinical studies have reported increased cytokines in serum and cerebrospinal fluid (CSF) in patients with epilepsy. Peltola et al.²⁸ measured plasma and CSF cytokines in 22 patients with newly developed tonic-clonic epilepsy and 18 controls, and found that patients with epilepsy had increased levels of IL-6 and IL-1 receptor antagonist in both plasma and CSF compared to the controls. Ravizza et al.²⁹ suggested an important role for IL-1 β in the mechanisms of hyperexcitability leading to the occurrence of epilepsy, and found that the number of IL-1 β -positive neurons was positively correlated with the frequency of epilepsy. Previous evidence has suggested the important roles of microglia and mast cells in neuroinflammation and related cytokine production, and reported that the synergic effect of microglia and mast cells may contribute to chronic neurodegenerative diseases and accelerate disease progression.^{13,14} Mast cells could move through normal brain, with rapid entry mediated via blood-brain barrier passage, and systemic inflammatory diseases further facilitated the entry.^{13,14,30} Entering the vicious cycle of neuroinflammation, mast cells produced a plethora of mediators, including biogenic amines (histamine, serotonin) and cytokines (IL-1 to IL-6, TNF- α , and IFN- γ).^{13,14} Furthermore, activated mast cells resulted in demyelination and induced apoptotic oligodendrocyte death.^{13,14}

Mast cells were thought to function primarily as effector cells for allergic diseases, including atopic dermatitis, asthma, and allergic rhinitis. The early phase of an atopic reaction is mediated predominantly by mast cells and Th₂ cytokines, in which IL-4, IL-6, and IL-13 drive immunoglobulin (Ig)-E production by promoting immunoglobulin class-switch recombination in B cells, and a cascade of pro-inflammatory agents, such as Th₁ immuneactive cytokines (i.e., IL-2, IL-3, NS TNF- α) and chemokines, are also

Table 2. Risk of developing epilepsy among patients with atopic dermatitis and the control group

	<18 years HR (95% CI)	18–64 years HR (95% CI)	≥65 years HR (95% CI)	Total HR (95% CI)
Atopic dermatitis, presence vs. absence ^a	3.29 (2.44–4.45)	1.79 (0.88–3.65)	1.27 (0.34–4.77)	2.91 (2.23–3.82)
Comorbidities, presence vs. absence				
Asthma	1.17 (0.90–1.52)	2.68 (0.97–7.39)	8.83 (2.24–34.84)	1.34 (1.04–1.72)
Allergic rhinitis	1.47 (1.12–1.94)	0.63 (0.26–1.53)	1.88 (0.52–6.77)	1.34 (1.04–1.73)
Allergic conjunctivitis	0.87 (0.68–1.13)	1.28 (0.54–3.06)	0.91 (0.18–4.47)	0.89 (0.70–1.14)
Cerebrovascular diseases	15.60 (5.33–45.70)	7.19 (2.95–17.51)	14.97 (3.02–74.34)	11.36 (6.09–21.21)
Head injury	2.73 (1.54–4.85)	2.60 (0.87–7.80)	NA	2.45 (1.50–4.02)
Meningitis and encephalitis	15.81 (9.02–27.73)	5.03 (0.56–45.58)	NA	13.19 (7.64–22.67)

HR, hazard ratio; CI, confidence interval; NA, not available. Bold type indicates statistical significance ($p < 0.05$).

^aAdjusted by demographic data and medical comorbidities and atopic dermatitis as a binary variable.

released sequentially.³¹ The oversecretion of proinflammatory cytokines during atopic reactions would penetrate the blood–brain barrier³² and activate neuroimmunologic mechanisms involving some specific neural circuits (i.e., anterior cingulate gyrus and insula) related to behavioral modulation.^{33–35} Furthermore, genetic studies have indicated the critical roles of polymorphisms of cytokine genes in the risk of atopic dermatitis. Gharagozlou et al.³⁶ reported a significant relationship between the increase in the frequency of the G allele and GG genotype at position –174 of IL-6 and the risk of atopic dermatitis. Behniafard et al.³⁷ demonstrated that the GG genotypes at the TNF- α gene at positions 238 and 308 were significantly associated with atopic dermatitis. Esparza-Gordillo et al.³⁸ investigated 318 genetic markers among 7,130 patients with atopic dermatitis and 9,253 control subjects, and found that a functional amino acid change in the IL-6 receptor (IL-6R Asp358Ala; rs2228145) was significantly associated with atopic dermatitis, and specifically predisposed the patient to the persistent form of atopic dermatitis.

In this study, we found a significant temporal association between atopic dermatitis and the risk of epilepsy, and further observed that allergic rhinitis and asthma were also related to the elevated risk of epilepsy. Several hypotheses may explain this association between atopic dermatitis and epilepsy. First, atopic dermatitis and epilepsy may share similar susceptible genes, such as cytokine genes and the de novo deletion of chromosome 22q13.2 mentioned in the introduction. Second, oversecretion of cytokines after a cycle of atopic reactions would penetrate the brain–blood barrier, and then contribute to the neuroinflammation and injure neuron cells. The chronic neuroinflammation and neuronal damage would further increase the susceptibility to epileptogenesis. Theoharides and Zhang³⁹ also suggested a possible role for treating neuroinflammation in the treatment of epilepsy. However, further studies would be required to investigate these hypotheses and elucidate the definite underlying mechanism linking atopic dermatitis, or a broader spectrum of atopy, and epilepsy.

Finally, compatible with the finding of Silverberg et al.⁴⁰ that children with allergic disease had more epilepsy in their lifetime than nonallergic children (odds ratio [OR] 1.79, 95% CI 1.37–2.33), our study also showed that only children with atopic dermatitis had an increased risk of developing epilepsy in later life after adjusting for demographic data and medical comorbidities. Silverberg et al. further found that severe atopic dermatitis (OR 23.89, 95% CI 1.34–11.32) was associated with even higher risk of epilepsy compared with mild/moderate disease.⁴⁰ The possible explanation may be that the majority of adults with epilepsy experience a childhood onset, and the incidence of the adulthood-onset epilepsy was much lower than the incidence of childhood-onset epilepsy.⁴

Some limitations of this study should be addressed here. First, the incidence of epilepsy may be underestimated

because only those individuals who sought medical help were enrolled. So, a problem of identification of the subjects may exist. However, the subjects enrolled in our study had board-certified physician diagnoses, yielding better diagnostic validity relative to the diagnoses by self-report questionnaire. Second, because of the limitation of NHIRD, we can identify the case subjects by only the ICD-9-CM code: 345 of epilepsy, further information such as syndrome level was not available. Third, the NHIRD did not provide some information, such as food allergy, family history, personal lifestyle, and environmental factors. Without this information, we were unable to examine their influence.

In conclusion, our results supported the elevated risk of developing epilepsy in later life of subjects with atopic dermatitis, especially children. Asthma and allergic rhinitis were also related to an increased risk of epilepsy. Further studies would be required to investigate the underlying pathophysiology between atopic dermatitis and epilepsy, and to further elucidate the possible relationship of the broader spectrum of atopy with epilepsy.

ACKNOWLEDGMENT

We thank Mr I-Fan Hu's friendship and support. The study was supported by grant from Taipei Veterans General Hospital (V103E10-001).

DISCLOSURE

All authors declare no conflict of interest. All authors have no financial relationships relevant to this article to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Chen et al, 2014, DOI: [10.1111/epi.12667](https://doi.org/10.1111/epi.12667)