

Allergy and Venous Thromboembolism: A Casual or Causative Association

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Abstract

Allergic diseases are very frequent conditions worldwide. The pathogenesis of allergic reactions and venous thromboembolism (VTE) shares several risk factors and predisposing conditions. In particular, the concentration of immunoglobulin E (IgE) is considerably increased in patients with allergic diseases, and this immunoglobulin exerts many prothrombotic and antifibrinolytic activities, especially through interaction with mast cells. Therefore, this narrative review is aimed to provide an overview of the current scientific evidence supporting a potential relationship between allergy and the risk of VTE. Although no prospective studies have been published so far, the evidence provided by six large cross-sectional studies and several case reports support the existence of an unquestionable epidemiological association between different allergic diseases (especially atopy, asthma, and celiac disease) and venous thrombosis. Two additional investigations reported that the concentration of IgE might predict the onset of severe complications of pulmonary embolism such as pulmonary infarction and pleural fluid accumulation. Therefore, the existence of a convincing epidemiologic link between allergy and VTE paves the way to future investigations aimed to establish whether the prevention or treatment of allergic diseases might be regarded as an effective measure to lower the risk of VTE.

Keywords

- thrombosis
- venous thromboembolism
- allergy
- asthma
- atopy

An Introduction to Allergy

The worldwide prevalence of allergy is dramatically increasing. According to recent statistics of the World Allergy Organization, allergic diseases include several conditions such as rhinitis, allergic conjunctivitis, asthma, (atopic) eczema, urticaria (hives), angioedema, and anaphylaxis (► **Table 1**).¹ Allergic rhinitis and its frequent complication rhinosinusitis are the results of an immunoglobulin E (IgE)-mediated inflammatory reaction affecting the nasal mucosa and exhibiting a prevalence comprised between 10 and 30% of the general population. Allergic conjunctivitis is another frequent allergic disease attributable to IgE sensitization to aeroallergens, which may lead to permanent ocular injury up

to loss of vision. Asthma, affecting up to 300 million people around the globe, is a chronic inflammatory disorder of the airways, which can be associated with various structural changes and ultimately leading to airway hyperresponsiveness and obstruction.¹ This condition is one of the most debilitating allergic disorders, since it dramatically impairs quality of life and affects all socioeconomic members of society. Atopy (i.e., a genetically determined inclination to developing IgE-mediated sensitivity to common aeroallergens) is the strongest predisposing condition for asthma.¹ Eczema, a condition anticipating the occurrence of more severe symptoms in atopic patients, is currently regarded as the most frequent inflammatory disease of the skin, which is also associated with considerable impairment in quality of

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Table 1 Clinical manifestations of allergy

- Rhinitis (and rhinosinusitis)
- Allergic conjunctivitis
- Asthma
- Eczema
- Urticaria
- Angioedema
- Anaphylaxis

life.¹ Urticaria, exhibiting a worldwide prevalence approximating 20% in the general population, is a self-limited condition characterized by the appearance of typical fleeting elevations of the skin (i.e., wheals) lasting nearly 24 hours, which can then progress toward angioedema or, more seriously, to anaphylaxis.¹ Angioedema comprises the development of deeper swellings of skin and mucous membranes of the lips, mouth, tongue, larynx, and pharynx. When the upper respiratory tract is involved, angioedema becomes a life-threatening medical emergency.¹ Anaphylaxis is a severe, rapidly developing and often life-threatening allergic condition, with an approximately 2% prevalence around the globe. Among the various allergic conditions, anaphylaxis is the most severe, since it is typically accompanied by dyspnea, hives or swelling, throat tightness, nausea, vomiting, hypotension, and often by dramatic cardiovascular impairment (i.e., dysrhythmia, coronary artery spasm, myocardial infarction up to cardiac arrest).¹

Pathogenesis of Venous Thromboembolism

Venous thromboembolism (VTE) is an acute and life-threatening disease, which is characterized by the onset of deep vein thrombosis (DVT), pulmonary embolism (PE), or the association of both.² Venous thrombosis is typically a multifactorial disorder, resulting from the association of several inherited and acquired conditions. The relative risk conferred by each predisposing factor varies widely. Indeed, the major acquired conditions include malignancy, major (especially orthopedic) surgery, prolonged immobilization, pregnancy and postpartum, trauma, and antiphospholipid antibodies (aPL), whereas deficiencies of natural anticoagulants (especially antithrombin, protein C, and protein S) are the stronger congenital risk factors.^{3,4} The relative contribution of additional conditions (i.e., obesity, infections, oral contraceptives, hyperhomocysteinemia, factor V Leiden, prothrombin gene mutation, among others) is still debated but unquestionably lower than that of the major risk factors (► **Table 2**).^{5–7}

As specifically regards the pathogenesis of VTE, it is now widely accepted that the original concept formulated by the German physician Rudolf Virchow in 1856 (i.e., the so-called “Virchow triad”⁸) should be considered as relevant now as when originally conceived. In brief, venous thrombosis conventionally originates from the combination of three synergic abnormalities: endothelial dysfunction, hemorheological abnormalities, and alterations of platelet biology and coagulation factors activity. Several lines of evidence suggest that

Table 2 Risk factors and predisposing condition for venous thromboembolism

- | |
|---|
| Major acquired conditions |
| ◦ Cancer |
| ◦ Major (especially orthopedic) surgery |
| ◦ Prolonged immobilization |
| ◦ Trauma |
| ◦ Pregnancy and postpartum |
| ◦ Antiphospholipid antibodies |
| Major inherited conditions |
| ◦ Antithrombin deficiency |
| ◦ Protein C deficiency |
| ◦ Protein S deficiency |
| Minor acquired conditions |
| ◦ Obesity |
| ◦ Infections |
| ◦ Oral contraceptives |
| ◦ Hyperhomocysteinemia |
| Minor inherited conditions |
| ◦ Factor V Leiden |
| ◦ Prothrombin gene mutation |

chronic inflammatory diseases such as inflammatory bowel disease,⁹ autoimmune disorders,¹⁰ and chronic obstructive pulmonary disease¹¹ may be associated with a procoagulant state, thereby enhancing the risk of venous thrombosis, especially during their active phase. Since allergy is a highly prevalent and life-long disease, this article aims to provide an overview of the current scientific evidence supporting a potential relationship between this condition and the risk of VTE.

Clinical Association between Allergy and Venous Thromboembolism

Clinical Investigations

The first study investigating the potential association between allergy and venous thrombosis was published by Farmer et al in 1999.¹² Briefly, data obtained from UK MediPlus (216,980 woman-years) and UK General Practice Research Database databases (840,485 woman-years in two studies) of the relationship between VTE and oral contraceptives were reviewed. Along with other significant associations, an excess number of cases of allergic patients was found in patients with VTE (17–19%) compared with controls (10–14%). In stepwise analysis, asthma was found to be a significant risk factor for VTE in both study populations, exhibiting an odds ratio (OR) of 1.9 (95% confidence interval [CI], 1.3–2.9) and 2.5 (95% CI, 1.6–3.8), respectively.

Another important investigation was published nearly 8 years after by Huerta et al.¹³ In that large prospective, nested case-control study, the prevalence of several risk factors for VTE was compared between 6,550 patients with VTE and a random sample of 10,000 matched healthy controls. The presence of asthma was found to be a modest but significant risk factor for VTE (OR, 1.22; 95% CI, 1.09–1.37), as well as for both DVT (OR, 1.15; 95% CI, 1.00–1.31) and PE (OR, 1.32; 95% CI, 1.15–1.53).

In a subsequent investigation, Undas et al performed a case-control study to compare the incidence of atopic disease among patients with VTE (129 patients aged 20–45 years; 87 with isolated DVT, 17 with isolated PE, and 25 with both DVT and PE) and a healthy control population with no history of VTE (144 subjects matched for age and gender, enrolled from hospital staff and students).¹⁴ The prevalence of atopic disease was found to be significantly higher in VTE cases (38%) than in controls (22%). Accordingly, atopic disease was found to be a significant risk factor for VTE, displaying an OR of 2.1 (95% CI, 1.21–3.50). Similar evidence was found for the prevalence of allergic rhinitis (30 vs. 19%; OR, 1.9; 95% CI, 1.07–3.30). The presence of asthma was also found to be a potential risk factor for VTE (OR, 1.60; 95% CI, 0.49–5.18), but the association did not reach statistical significance due to the very low number of VTE events identified in both cases ($n = 7$; 5.4%) and controls ($n = 5$; 3.5%). Interestingly, the use of oral corticosteroids was not found to be significantly associated with VTE (OR, 2.34; 95% CI, 0.77–7.06) due to the low number of VTE in cases ($n = 5$; 3.9%) and controls ($n = 3$; 2.1%) using these drugs. It is also noteworthy that the presence of some common prothrombotic conditions such as factor V Leiden, prothrombin gene mutation, and aPL was similar between VTE patients with or without atopic disease, thus suggesting that the thrombotic risk in atopic patients may be independent from the presence of thrombophilia.

Cazzola et al performed a population-based, case-control retrospective study using information obtained from the Italian Health Search Database,¹⁵ aiming to identify the most significant comorbid medical illness in patients with asthma. The final study population included 909,638 subjects (479,676 females and 429,962 males) aged 14 years or older, 55,500 (6.1%) of whom suffering from asthma. The prevalence of PE was found to be substantially higher in patients with asthma than in those without (0.26 vs. 0.17%). In multivariate analysis, asthma was found to be a significant risk factor for PE (OR, 1.61; 95% CI, 1.36–1.86).

Majoer et al performed a retrospective study including 648 patients with asthma (283 with severe asthma and 365 patients with mild-to-moderate asthma), who were asked to complete a standardized questionnaire about previous episodes of VTE and related risk factors.¹⁶ Overall, 35 episodes of VTE could be recorded (16 DVT and 19 PE). Although the incidence of DVT was moderately but not significantly higher in patients with severe asthma (0.36 per 1,000 person-years; 95% CI, 0.04–0.67) or mild-to-moderate asthma (0.61 per 1,000 person-years; 95% CI, 0.25–0.98) compared with the general population (0.28 per 1,000 person-years; 95% CI, 0.10–0.47), the incidence of PE was found to be consistently and significantly higher in patients with severe asthma (0.93 per 1,000 person-years; 95% CI, 0.42–1.44) and in those with mild-to-moderate asthma (0.33 per 1,000 person-years; 95% CI, 0.07–0.60) compared with the general population (0.18 per 1,000 person-years; 95% CI, 0.03–0.33). Accordingly, the standardized risk ratios for VTE were 8.93 (95% CI, 4.62–15.63) in patients with severe asthma and 3.97 (95% CI, 0.97–9.12) in those with mild-to-moderate asthma, respectively. In

multivariate analysis, severe asthma (hazard ratio [HR], 3.33; 95% CI, 1.16–9.93) and use of oral corticosteroids (HR, 2.82; 95% CI, 1.09–7.30) were found to be independently associated with PE.

In an ensuing study, Chung et al performed a large nationwide population cohort investigation in Taiwan, which included 31,356 patients with asthma and 125,157 controls subjects without asthma selected from the general population.¹⁷ The incidence rate of PE was found to be approximately threefold higher in patients with asthma than in those without (10.2 vs. 3.1 per 100,000 person-years). Accordingly, the adjusted HR for PE in patients with asthma was 3.24 (95% CI, 1.74–6.01). The asthma-related risk of PE was also found to be considerably higher in male than in female patients (HR, 3.20; 95% CI, 1.50–6.82), in patients aged 65 years or older compared with those aged 50 years or younger (HR, 20.0; 95% CI, 6.54–61.1), and in patients with cancer compared with those without (HR, 3.26; 95% CI, 1.43–7.45). Interestingly, a highly significant correlation was observed between severity of asthma and risk of PE, wherein the HR for PE was 8.39 (95% CI, 3.92–18.0) in patients with four or more emergency room visits per year for asthma compared with those with one to two emergency room visits per year, and 4.16 (95% CI, 1.39–12.4) in patients with one to two hospital admissions per year for asthma compared with those with no hospital admissions.

Interesting evidence also emerged from another study including 46 patients (27 females and 19 males) with acute PE, who were followed up to 4 months after the diagnosis.¹⁸ The concentration of serum IgE was found to be nearly fivefold higher in patients with submassive PE and pulmonary infarction (508 U/mL) compared to those with submassive PE but without pulmonary infarction (117 U/mL), thus suggesting that allergy may also play a role in determining the severity of venous thrombosis.

The potential interplay between IgE and thrombosis was confirmed in another small study including 14 patients with PE,¹⁹ in whom high serum IgE concentration at the time of PE diagnosis was found to be a predictor of pulmonary infarction and pleural fluid accumulation.

Case Reports

Beside the case-control studies previously described, several case reports have been published on putative (potentially causal) association between allergic diseases and venous thrombosis.

Gabrielli et al described the case of a 53-year-old man who was admitted to the hospital for pain and edema of the left leg lasting for 6 days and recent onset of chest pain.²⁰ Radiological investigations were suggestive for the presence of DVT and PE. Clinical history and a comprehensive screening for thrombophilia failed to reveal the existence of prothrombotic risk factors. However, additional investigations (i.e., antiendomysial antibodies and celiac biopsy) were consistent with a diagnosis of celiac disease.

Beyan et al reported on the case of a 44-year-old man, who was admitted to the hospital due to diarrhea lasting for 3 months.²¹ A diagnosis of celiac disease was finally reached and a gluten-free diet was initiated. Nevertheless, a marked

swelling, erythema, and pain developed in the left leg on the 7th day of hospitalization, which led to the diagnosis of left proximal DVT. Interestingly, no congenital or acquired thrombophilic conditions could be identified.

Liu et al reported the case of a patient with Kimura disease (i.e., an indolent chronic inflammatory disease characterized by the presence of massive peripheral blood eosinophilia and elevated values of serum IgE),²² who was admitted with life-threatening visceral venous thromboses with no evidence of acquired or inherited thrombophilic conditions.

Baryshnikov et al described the case of a young woman with gluten-sensitivity celiac disease,²³ who developed recurrent lower extremity DVT. Interestingly, a thrombophilia screening revealed hyperhomocysteinemia (possibly due to combined deficiencies of vitamin B and folic acid) along with heterozygous deficit of protein S.

Jones et al described the case of a 33-year-old man suffering from severe eosinophilic esophagitis,²⁴ which was virtually unresponsive to oral budesonide therapy. The patient developed isolated PE in the absence of known congenital or acquired risk factors for VTE. The PE episode was therefore attributed to the inflammation-mediated hypercoagulability and IgE-mediated platelet activation, which both characterize eosinophilic esophagitis.

Recently, Okur et al reported on a case of a 45-year-old woman with a history of recurrent VTE,²⁵ who was admitted to the emergency department with an episode of DVT of the popliteal vein complicated by PE of the right main pulmonary artery and its major descending branch. Interestingly, no significant risk factors for VTE could be identified other than asthma.

Conclusions

Several lines of evidence now attest that the pathogenesis of VTE is essentially multifactorial. Venous thrombotic events typically begin in a subject bearing predisposing (either congenital or acquired) prothrombotic conditions, when a triggering factor propels that patient over a threshold, which ultimately precipitates the development of thrombosis. The number of putative prothrombotic conditions and triggering factors continues to grow along with our major understanding of biochemistry and biology of thrombotic disorders.²⁶ In particular, strenuous physical exercise, drug abuse, sneezing and coughing attacks, migraine, defecation, sexual activity, and even vacation and holidays have been indicated as potential but often unsuspected triggers of VTE.^{27,28}

Since chronic diseases have been frequently associated with an increased risk of venous thrombosis, it would not be surprising to find a significant relation between allergy and VTE, considering the long-lasting nature of the former condition. Further support to investigate the link between allergic diseases and venous thrombosis comes from the challenge of diagnosing PE in patients with asthma. In fact, it has long been known that bronchoconstriction may be a consequence of PE, so that wheezing may be occasionally present and lead to misdiagnosing bronchial asthma rather than PE in an asthmatic patient.²⁹

Although no prospective studies have been published so far to the best of our knowledge, the evidence provided by six large cross-sectional studies (►Table 3) and several case reports support the existence of an unquestionable epidemiological association between different allergic diseases and venous thrombosis. This putative link is further reinforced by two additional investigations reporting that the concentration of IgEs predicts some severe complications of PE, such as pulmonary infarction and pleural fluid accumulation (►Table 3). Although it seems therefore reasonable to conclude that allergy and venous thrombosis are epidemiologically linked, a crucial issue remains, which is to establish whether allergic diseases are “causative” independent risk or triggering factors for venous thrombosis, or rather their “causal” association with VTE, especially with PE, may be alternatively mediated by various demographical, clinical, or therapeutic factors. Although the results of the case-control studies published so far apparently suggest that this relationship may be independent from the presence of acquired or congenital prothrombotic conditions, as well as from the conventional therapeutic management of allergic patients, an association has been convincingly demonstrated between VTE and corticosteroid therapy, a very frequent treatment in patients with allergic diseases.³⁰ A large population-based case-control study using nationwide Danish databases reported that systemic glucocorticoids administration was significantly associated with VTE in present (adjusted incidence rate ratios [IRR], 2.3; 95% CI, 2.2–2.4), continuing (IRR, 2.0; 95% CI, 1.9–2.2) as well as in recent (IRR, 1.18; 95% CI, 1.10–1.26) users, but not in former users of these drugs (IRR, 0.94; 95% CI 0.90–0.99).³¹ Another recent retrospective study including 15,100 adults with inflammatory bowel disease confirmed this association,³² and concluded that corticosteroid administration conferred an approximately fivefold increased risk of VTE compared with biologic agent therapy. According to these data, it cannot be ruled out that the association between allergic diseases and venous thrombosis may be at least in part mediated or amplified by glucocorticoid therapy, as also confirmed by the enhanced risk of VTE in patients with Cushing syndrome.³³

As specifically regards the potential causal link between allergy and venous thrombosis, several pathogenetic mechanisms can be advocated (►Fig. 1). More specifically, IgE exerts some prothrombotic and antifibrinolytic activities, especially through its interaction with mast cells. These mechanisms basically include the capability of triggering platelet activation and aggregation, as well as promoting the expression and release into the circulation of tissue factor and plasminogen activator inhibitor 1.³⁴ Allergic inflammation has also been advocated as a potential mechanism contributing to the development of a prothrombotic milieu in patients with allergic diseases, especially asthma,³⁵ whereas the activity of both coagulation factor VIII and von Willebrand factor or independent risk factors for thrombosis when expressed in excess^{36,37} were found to be increased in children with asthma—especially in those with severe asthma—compared with healthy controls.³⁸ Last but not least, the fact that asthmatic patients are usually less physically active

Table 3 Summary of clinical studies about the association between allergy and VTE

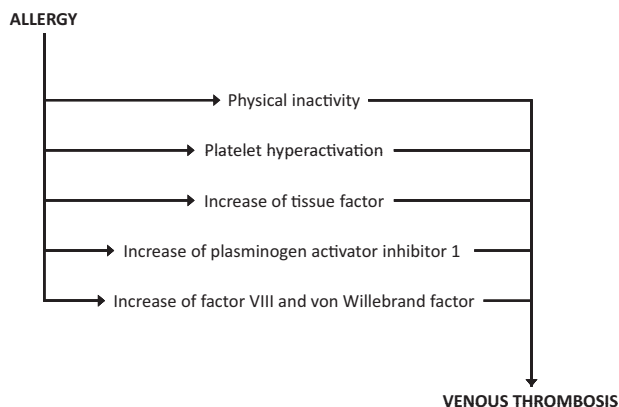
Authors	Study design	Population	Outcome	References
Farmer et al, 1999	2 Case-control studies	840,485 woman-years and 216,980 woman-years in two studies	Asthma significant risk factor for VTE, with OR of 1.9 (95% CI, 1.3–2.9) and 2.5 (95% CI, 1.6–3.8)	12
Huerta et al, 2007	Nested, case-control study	6,550 patients with VTE and 10,222 matched healthy controls	Asthma significant risk factor for VTE (OR, 1.22; 95% CI, 1.09–1.37), deep vein thrombosis (OR, 1.15; 95% CI, 1.00–1.31), and pulmonary embolism (OR, 1.32; 95% CI, 1.15–1.53)	13
Undas et al, 2011	Case-control study	129 patients with VTE and 144 healthy controls	Atopy independently associated with VTE (OR, 2.1; 95% CI, 1.21–3.50) Allergic rhinitis independently associated with VTE (OR 1.9; 95% CI, 1.07–3.30)	14
Cazzola et al, 2011	Population-based, case-control retrospective study	909,638 subjects, 55,500 (6.1%) of whom suffering from asthma	Asthma independently associated with pulmonary embolism (OR, 1.61; 95% CI, 1.36–1.86)	15
Majoor et al, 2013	Retrospective, case-control study	648 patients with asthma, 35 with VTE	Severe asthma independently associated with pulmonary embolism (HR, 2.82; 95% CI, 1.09–7.30)	16
Chung et al, 2014	Population, case-control study	31,356 patients with asthma and 125,157 controls subjects without asthma	Asthma independently associated with pulmonary embolism (HR, 3.24; 95% CI, 1.74–6.01)	17
Doru et al, 2004	Nested case-control study	46 patients with pulmonary embolism	Serum levels of immunoglobulins E substantially higher in patients with pulmonary infarction	18
Takekawa et al, 1993	Nested case-control study	14 patients with pulmonary embolism	Baseline serum immunoglobulins E concentration predicted pulmonary infarction and pleural fluid accumulation	19

Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio; VTE, venous thromboembolism.

than the general population without this condition cannot be discounted as a contributing factor given that inactivity is a well-recognized risk factor for VTE.³⁹

In conclusion, although the published evidence so far remains limited to cross-sectional studies or case reports, it

seems somehow undeniable that an epidemiological relationship does exist between allergic diseases and venous thrombosis, thus paving the way to future investigations aimed to establish whether the prevention or treatment of allergic diseases may be regarded as an effective measure to lower the risk of VTE.

**Fig. 1** Potential mechanisms for pathogenesis of venous thrombosis in patients with allergic diseases.

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