

Table 1 (continued)

Ethnicity, age (y), and sex	Clinical presentation & co-morbidities	Skin prick test and prick to prick test results (mm), positive result ≥ 3 mm	Specific IgE blood test results (KUa/L) positive result ≥ 0.35 KUa/L
Pt 8 White British 28F	- Itchy scalp, widespread hives, facial swelling, and difficulty breathing after drinking red wine and eating nonspecific snacks - Itchy palms, periorbital angioedema, and urticaria 10 minutes after consuming a chocolate bar with nuts - Itchy palms, tight throat, and rash after eating melon and red grapes - Lip swelling after eating spicy chicken nuggets and paprika-flavored potato snack Co-morbidities: Mild Seasonal allergic rhinitis	Positive: Peanut (3), almond (3), pecan (3), strawberry (3), peach (3), hazelnut (5), paprika (6), prick to prick to raw red pepper (4), prick to prick to raw yellow pepper (3), prick to prick to raw chilli (3) Negative: Melon, kiwi, apple, pine nuts, pistachio, sesame, walnut, cashew nut, Brazil nut.	Positive: Ara h 9 (0.44), Pru p 3 (0.72), grape (0.39), Mal d 3 (0.85), hazelnut (0.68), almond (0.74), walnut (0.35) Negative: peanut, cashew nut, Brazil nut, paprika (0.31), Mal d 1, Cor a 1, Cor a 8, Cor a 9, Cor a 14, Pru p 1, Pru p 4, Jug r 1, Jug r 3 (0.34). Total IgE: 25

F, female; IgE, immunoglobulin E; M, male; nsLTP; non-specific lipid transfer protein; Pt, patient.

^aHazelnut components = Cor a 1, Cor a 8, Cor a 9, Cor a 14. Peach components = Pru p 1, Pru p 3, Pru p 4. Peanut components = Ara h 1, Ara h 2, Ara h 3, Ara h 6, Ara h 8, Ara h 9. Walnut components = Jug r 1, Jug r 3. Apple components = Mal d 1, Mal d 3. Total IgE range = 0–81 KU/L. Tryptase normal range = 2–14 μ g/L.

widespread, not geographically restricted, and also is seen in the north of England. Interestingly the patients described by Skypala et al only had reactions to tree nuts, peanuts, apples, stone fruits, and tomatoes.⁸ The patients in this case series reacted to peanuts, tree nuts, stoned fruits, raspberry, strawberry, blueberry, tomatoes, pumpkin, blackberry, grape, melon, lettuce, apple, honeydew melon, paprika, corn, and blackcurrant.

The prevalence of this condition in adults based on the Preston experience is 0.6 adult cases per 100,000 adults in the United Kingdom, although this maybe an underestimation. This is based on the catchment population served by the Preston Adult Allergy Department, which is 1.3 million adults. We believe that this is the first report of cases of nsLTP allergy in the most northern part of Europe.

In conclusion, these findings highlight the importance of investigating patients who present with multiple severe and systemic food allergies for nsLTP allergy regardless of geography. The patients described here were counseled about allergen avoidance and were given a specific leaflet designed in-house for patients with nsLTP allergy, highlighting safe and at-risk foods. These patients were also prescribed adrenaline pens, and each was provided with a tailored anaphylaxis action plan on how to deal with allergic reactions.

Ariharan Anantharachagan, MBChB, MRCP, MSc, FRCPATH^{*,†}

Roweida Sammour, MBChB[‡]

Pavaladurai Vijayadurai, MBBS, FRCP, FRCPATH^{*}

^{*}Department of Allergy and Clinical Immunology, Lancashire Teaching Hospitals, NHS Foundation Trust, Preston, United Kingdom

[†]Department of Immunology, Cambridge University Hospitals, NHS Foundation Trust, Cambridge, United Kingdom

[‡]Department of Medicine, Royal Albert Edward Infirmary
Wrightington Wigan and Leigh, NHS Foundation Trust, Wigan
United Kingdom
ariharan.anantharachagan@lthtr.nhs.uk

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Association of atopic dermatitis with increased risk of anaphylaxis to egg and milk

Although atopic dermatitis (AD) has been associated with increased risk of food allergy (FA), this association is not fully understood, and the predictors of severe reactions to foods are not clear. In a review of 18 population-controlled studies, the rate of food sensitization

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was up to 6 times higher in patients with AD vs healthy controls.¹ A recent study identified a potential physiologic mechanism by demonstrating increased skin barrier dysfunction, measured by increased transepidermal water loss and reduced skin filaggrin levels, in patients with AD and FA.² These defects are hypothesized to facilitate penetration of food proteins through the skin and induce sensitization.² Although the development of FA is associated with more severe AD, it is not well known how the presence of AD



Table 1

Characteristics and Prevalence of Anaphylaxis in Patients With Food Allergy With and Without a History of Atopic Dermatitis (AD)

Group	Total IgE, mean (SD), log	Specific IgE, mean (SD), kUA/L	Wheal size, mean (SD), mm	Anaphylaxis, No./total No. (%)
Peanut allergy				
No AD (n = 62)	3.65 (1.27) ^a	29.3 (37.7)	12.0 (7.7)	14/62 (23)
AD (n = 158)	2.93 (0.60) ^a	36.5 (38.9)	12.7 (8.1)	43/158 (27)
Egg allergy				
No AD (n = 35)	2.22 (0.78) ^a	15.0 (29.8)	7.1 (4.2)	4/35 (11) ^a
AD (n = 45)	2.86 (0.68) ^a	21.2 (32.3)	7.4 (5.0)	21/45 (47) ^a
Milk allergy				
No AD (n = 21)	2.00 (0.68) ^a	18.4 (34.8)	6.5 (5.6)	4/21 (19) ^b
AD (n = 26)	2.92 (0.71) ^a	25.0 (34.9)	7.9 (4.9)	13/26 (50) ^b

^a*P* < .001.^b*P* = .04.

affects the severity of FA. We aimed to elucidate how food allergies differ between children with and without AD. Our hypothesis was that children with AD would have more severe FA as defined by increased rates of anaphylaxis.

We searched our institutional research database for patients aged 0 to 18 years who were diagnosed with FA (peanut, cow's milk, and/or egg) from March 2008 to October 2017. A retrospective medical record review identified a total of 326 patients with FA who did not have a current or past history of AD based on *International Classification of Diseases* coding and medical record documentation. FA was confirmed by documented history of an immediate clinical reaction and positive skin test and/or blood test results that met the criteria for a 95% or greater positive predictive value.³ The FA with no AD group was compared with a group of 326 patients with FA and AD who were matched by type of food allergy, age, and race/ethnicity. Selection bias was minimized by including all patients without AD identified in our database search and matching patients with AD from a randomized list. Collected information included total IgE levels, food specific IgE (sIgE) levels, food skin prick test (SPT) results, baked milk and baked egg tolerance, and comorbid atopic conditions. A total of 138 patients were excluded because of incomplete data. History of anaphylaxis was determined by documentation of a clinical reaction within 2 hours of eating a known food allergen with 2 or more body systems affected, airway compromise, or hypotension based on National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria.⁴ Anaphylaxis events could be attributable to unintentional ingestion or oral food challenge. History of no anaphylaxis was determined by clear documentation of such, and 167 patients with unclear documentation were excluded from this analysis.

Egg and milk allergic patients with AD exhibited increased rates of anaphylaxis compared with similar patients without AD (47% vs 11%, *P* < .001, for egg and 50% vs 19%, *P* = .04, for milk) (Table 1). Peanut allergic patients with and without AD had similar rates of anaphylaxis (27% vs 23%, *P* = .61). History of baked milk and baked egg tolerance in the AD and no AD groups was not significantly different between groups (83% vs 61%, *n* = 24, and 82% vs 67%, *n* = 50). Total IgE levels were significantly increased in the AD compared with the no AD populations for egg and milk and decreased for peanut (Table 1). Food sIgE and SPT results were similar between the groups. More patients with ADA had allergic rhinitis compared with the patients without AD (63% vs 39%, *P* < .001), but similar proportions had asthma (59% vs 55%, *P* = .41). The Fisher exact test was used for the comparisons.

Currently, the factors that influence the severity of food allergy are incompletely understood. Increased age in children and poorly controlled asthma are associated with increased severity.⁵ A recent

study found that for cow's milk, increased sIgE, SPT, and family history of AD predicted increased reaction severity, in contrast to peanut, which had little predictability.⁶ Our data similarly suggest that a personal history of AD has a significant association with the rate of anaphylaxis for certain food allergies but not others. In the case of egg and milk allergies, pediatric patients with AD appear to be 4.3 and 2.6 times more likely, respectively, to have anaphylaxis compared with their counterparts without AD. Alternatively, the presence or absence of AD does not seem to make a significant difference in the rate of anaphylaxis in peanut allergic patients. This finding may suggest that skin barrier dysfunction plays a role in the severity of FA. However, this is not universal to all food antigens, and other mechanisms are likely important in the association of anaphylaxis with a particular food.

Rates of tolerance to baked egg and baked milk were similarly high across groups and trended toward increased tolerance in the AD group. Increased total IgE in the egg and milk allergic AD groups may support a link between T_H2 polarization and FA severity, particularly because this differed from the peanut AD group. sIgE and SPT results were similar between groups with and without AD, which is consistent with the literature reporting little overall association between these test levels and reaction severity.⁷ AD was also associated with increased allergic rhinitis, supporting a propensity to the atopic march as previously described.⁸

Admittedly, anaphylaxis history is subjectively assessed and often not well documented, making it difficult to study. By retrospectively applying the NIAID/FAAN criteria to clinical documentation, many patients were excluded from our analysis, a necessary measure to obtain the most accurate picture. Another limitation is the inability to determine the amount of food protein that triggered anaphylaxis. However, recent literature recommends that dose sensitivity and reaction severity should be considered separate in estimating risk.⁵ Dose was previously found to be a predictor of severity for peanut but not milk or egg.⁶ Additional studies are needed to corroborate these results, ideally prospectively and with a large, multicenter patient population. Other foods, such as soy, wheat, and tree nuts, should also be investigated, and we did not examine whether the severity of AD affects anaphylaxis risk.

In summary, our results suggest that patients with AD and egg or milk allergy are at significantly higher risk for anaphylaxis compared with patients without AD. Practitioners should consider AD an additional risk factor for severe reactions when counseling patients about egg or milk allergy and determining the safety of oral food challenges.

Bryce C. Hoffman, MD*

Shannon Garcia, BA*

Douglas C. Everett, PhD†

Donald Y.M. Leung, PhD*

Christine B. Cho, MD*

*Division of Allergy and Immunology, Department of Pediatrics
National Jewish Health, Denver, Colorado†Department of Biostatistics, National Jewish Health, Denver, Colorado
leungd@njhealth.org

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Systemic capillary leak syndrome a rare disease becoming increasingly recognized



Idiopathic systemic capillary leak syndrome (SCLS) is a rare disorder characterized by recurrent episodes of hypotensive shock caused by vascular hyperpermeability. Since the disorder was first described in 1960, fewer than 300 cases have been reported. Systemic capillary leak syndrome is a diagnosis of exclusion, and the differential diagnosis is broad. Once a diagnosis is made, clear guidelines for the management and prevention of episodes are lacking, often leading to delays in care.

A 66-year-old woman was traveling on a cruise ship when she developed 2 to 3 days of swelling in her feet and face. She became lightheaded with near syncope and was taken to a local hospital. Medical history included a hospital admission 3 months before, when she presented to her community hospital with shortness of breath and was found to have a pericardial effusion that was thought to be attributable to viral myocarditis. The patient also recalled a previous episode 6 months before admission of total body edema, during which she did not seek medical care.

On admission to the hospital, the patient had severe hypotension and hypovolemia. Laboratory evaluation was notable for hypoalbuminemia (2.9 g/dL) and increased hemoglobin (>20 g/dL). Infectious workup was negative, and computed tomography scans of the chest and abdomen along with transthoracic echocardiogram were unremarkable. The patient was treated with aggressive intravenous fluids and norepinephrine, with improvement in her hemodynamics, and she was discharged home without a clear diagnosis. Shortly after returning home from Europe, the patient developed significant edema in her eyelids, face, and feet. She was treated with intravenous furosemide and discharged with a 14-day course of oral furosemide. She was seen by the allergy/immunology department for a presumptive diagnosis of idiopathic SCLS, and she underwent extensive evaluation to rule out other diagnoses and secondary causes. Quantitative immunoglobulins, hepatitis C antibody, complement levels, urinalysis, serum protein electrophoresis, urine protein electrophoresis, serum immunofixation, urine immunofixation, and cardiac magnetic resonance imaging were all normal. She was recommended to start intravenous immunoglobulin (IVIG) as an outpatient.

The patient had difficulty obtaining insurance approval for IVIG treatment, which resulted in a several-month delay in initiation of therapy. During this time, she was hospitalized with a flare of SCLS. She received 2 g/kg IVIG during her acute hospitalization, along with intravenous furosemide, with improvement in her edema. After hospital discharge, the patient received insurance authorization to begin monthly IVIG prophylaxis. She has been maintained on 1 g/kg IVIG every 4 weeks at a local infusion center without any recurrent flares.

Systemic capillary leak syndrome is described as recurrent episodes of unexplained generalized edema and hypotension in association with hypoalbuminemia and hemoconcentration. Systemic capillary leak syndrome occurs sporadically and has most commonly been described in middle-aged white adults, with equal

sex distribution. An increase in the number of reported cases has been seen over the last 15 years, likely because of improved identification of the disease.¹

During acute episodes, patients develop anasarca caused by plasma extravasation. This has been termed the “leak phase,” and it may last several days. Complications of acute vascular leak occur because of tissue hypoperfusion, hemoconcentration, and peripheral edema. Compartment syndrome, which arises from massive peripheral edema during the leak phase, can lead to rhabdomyolysis, with increases in creatinine phosphokinase and potential renal failure, often necessitating fasciotomy.² Thrombosis, pleural and pericardial effusions, and ascites also may occur during the leak phase. During the post-leak phase, which typically occurs 48 to 96 hours after the initial attack, fluids are mobilized from peripheral tissues into the intravascular space, with normalization of circulation. Cardiovascular overload during the post-leak phase is the most common cause of death from SCLS.² The frequency of attacks is highly variable and ranges from once every 10 years to once every 3 to 5 days.

The diagnostic criteria for SCLS are described as a triad of hypotension (usually systolic blood pressure < 90 mmHg), hemoconcentration (hematocrit >49% to 50% in men and 43% to 45% in women), and hypoalbuminemia (<3.0 g/dL). A characteristic finding, although not required for the diagnosis, is the presence of paraprotein in the blood, or monoclonal gammopathy of unknown significance. There are known secondary causes of SCLS such as hepatitis C, malignancy, chemotherapeutic agents, and other viral illnesses.^{3–5} The differential diagnosis for SCLS is broad (Table 1), given the multitude of disorders with overlapping clinical and laboratory features that often results in misdiagnosis. In 1 review, the mean time spent on diagnosis after the first attack of SCLS was 7.9 months.¹

The pathogenesis of SCLS remains unknown, but several mediators have been implicated in the development of increased vascular permeability and subsequent capillary leak, including cytokines, leukotrienes, vascular endothelial growth factor and complement.³

Supportive care with intravenous fluids is the mainstay for treatment of acute episodes of SCLS. During the post-leak phase, diuresis is used to prevent pulmonary edema. Prophylactic treatment is empiric and based on observational studies. Long-term prophylaxis with IVIG administered monthly has been shown to reduce the severity and the frequency of episodes and has significantly improved the survival rate in most patients.⁶ Methylxanthines and beta agonists also have been used in combination with IVIG, although with unclear benefit.⁷ The mechanism of action of IVIG is unclear, but it is thought to be attributable to anti-idiotypic effects on paraprotein, neutralization of proinflammatory cytokines, and immunomodulatory effects.⁸ Dosing varies from 0.4 g/kg/month to 2 g/kg/month. In a European registry of 18 patients, 44% experienced no recurrent attacks while receiving IVIG prophylaxis.⁹ In another study reporting on a large cohort of patients with monoclonal gammopathy-associated SCLS, 5- and 10-year survival rates were 78% and 69%. The IVIG prophylaxis was the primary factor associated with survival.¹⁰

This case demonstrates that SCLS should be considered as an underlying diagnosis in patients who present with cyclical edema and