EMJ ALLERGY & IMMUNOLOGY

European Edition — Vol. 5.1 August 2020 emjreviews.com

+ EAACI CONGRESS 2020

Reviewed

+ INTERVIEWS

EAACI Past-Presidents Prof Dr. Hab. Ioana Agache and Prof Antonella Muraro speak about their presidential terms and key topics in allergy and immunology.

+ ABSTRACT REVIEWS

Reviews of abstracts presented at EAACI 2020, covering topics such as asthma, the skin mycobiome, and viral bronchiolitis.

+ EDITOR'S PICK

The Psychosocial Impact of Adolescent Food Allergy: A Review of The Literature

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"We hope that EMJ Allergy & Immunology 5.1, and future publications, will inspire new research ideas contributing to advancements in the field"

Spencer Gore, CEO

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Aims and Scope

EMJ is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

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This Publication

EMJ Allergy & Immunology is published once a year. For subscription details please visit: www.emjreviews.com

ISSN 2398-9130

Front cover and contents photograph: London, UK.

EMJ Allergy. 5.1

Welcome

Dear readers and contributors,

It is with great pleasure that I welcome you to this year's issue of the *EMJ Allergy & Immunology* eJournal, a collection of high-quality, hand-picked articles spanning various aspects of the field. Our devotion to providing thought-stimulating content to healthcare professionals worldwide is conspicuous throughout this compilation of original research, review articles, and case reports, and we truly hope that you immerse yourself into all *EMJ Allergy & Immunology 5.1* has to offer.

Originally due to be held in London, UK, this year's European Academy of Allergy and Clinical Immunology (EAACI) annual congress was held online as a result of the COVID-19 pandemic. Challenging times call for creative solutions and therefore, "bridging innovations into allergy and asthma prevention" was an appropriate theme for EAACI Digital Congress 2020. Our congress review will provide an overview of the latest research trends in the field, including the connection between air pollution and COVID-19 severity, and novel guidelines introduced for the use of biologics in patients with severe asthma.

We are also delighted to provide a diverse range of abstract summaries of research presented at the congress, along with interviews with two recent EAACI Past-Presidents, Prof Dr. Hab. Ioana Agache and Prof Antonella Muraro, who discuss their presidential terms and current contributions to the field.

The scientific content within these pages is truly fantastic, spanning from the psychological impact of food allergy on adolescents to primary immune deficiency disorders, and more. Despite the continued research and efforts within the field of allergy and immunology, an increased prevalence of allergic and immunologic diseases exists. We hope that *EMJ Allergy & Immunology 5.1*, and future publications, will inspire new research ideas contributing to advancements in the field. Finally, I would like to acknowledge everyone involved in the production of this wonderful edition and extend a special thank you to our respected readers for your continuous support.

Spencer Gore

Chief Executive Officer, EMG-Health

PRESENT IN ~50%[a] TO 70%[b] OF YOUR ADULT ASTHMA PATIENTS,

TYPE 2 INFLAMMATION IS HIGHLY HETEROGENEOUS AND A PREDICTOR OF RISK FOR FUTURE EXACERBATIONS[1-4]

IDENTIFY

Type 2 inflammation in asthma

HETEROGENEITY

Encompasses several phenotypes[2]:

- Allergen-driven
- Mixed eosinophilic and allergen-driven
- Eosinophilic

SIMPLE IDENTIFICATION

Identifiable by one or more of the following criteria[5]:

- ✓ Elevated EOS
- ✓ Allergen-driven
- ✓ Elevated FeNO
- ✓ OCS-dependency

EOS, eosinophils; **FeNO**, fractional exhaled nitric oxide; **OCS**, oral corticosteroid.

TARGET

Cytokines IL-4, IL-5 and IL-13 are key drivers of type 2 inflammation in asthma[6-8]

	IL-4	IL-13	IL-5
Th2 cell differentiation	●		
B-cell class switching and IgE production	●	●	
Eosinophil recruitment and trafficking to tissue	●	●	●
Eosinophil differentiation in bone marrow			●
Mucus production and goblet cell hyperplasia		●	
Smooth muscle hypertrophy and tissue remodeling	●	●	

IL-4 and IL-13 have distinct and overlapping roles with a broad impact on asthma symptoms[7,8]

TREAT

TO REDUCE

Exacerbations

Oral corticosteroids

TO IMPROVE

Lung function

Quality of life

Target and treat type 2 inflammation holistically to achieve optimal asthma control[1,5]

[a]N=205.
[b]N=37.

References: 1. Dunican EM, Fahy JV. The role of type 2 inflammation in the pathogenesis of asthma exacerbations. *Ann Am Thorac Soc.* 2015;12(suppl 2):S144-S149. **2.** Rogliani P, Calzetta L, Matera MG, et al. Severe asthma and biological therapy: when, which, and for whom [published online ahead of print December 25, 2019]. *Pulm Ther.* doi:10.1007/s41030-019-00109-1 **3.** Fahy JV. Type 2 inflammation in asthma-present in most, absent in many. *Nat Rev Immunol.* 2015;15(1):57-65. **4.** Peters MC, Mekonnen ZK, Yuan S, Bhakta NR, Woodruff PG, Fahy JV. Measures of gene expression in sputum cells can identify TH2-high and TH2-low subtypes of asthma. *J Allergy Clin Immunol.* 2014;133(2):388-394. **5.** Global Initiative for Asthma. Difficult-to-treat & severe asthma in adolescent and adult patients, 2020. https://ginasthma.org/wp-content/uploads/2020/04/GINA-2020-full-report_-final-_wms.pdf. Accessed April 14, 2020. **6.** Gandhi NA, Bennett BL, Graham NM, Pirozzi G, Stahl N, Yancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. *Nat Rev Drug Discov.* 2016;15(1):35-50. **7.** Robinson D, Humbert M, Buhl R, et al. Revisiting type 2-high and type 2-low airway inflammation in asthma: current knowledge and therapeutic implications. *Clin Exp Allergy.* 2017;47(2):161-175. **8.** Hammad H, Lambrecht BN. Dendritic cells and epithelial cells: linking innate and adaptive immunity in asthma. *Nat Rev Immunol.* 2008;8(3):193-204.

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Foreword

Dear Readers,

It is time to present to you the 2020 issue of *EMJ Allergy & Immunology*.

The European Academy of Allergy and Clinical Immunology (EAACI) Digital Congress 2020 was for the first time presented worldwide with the help of a digital platform. Thanks to all the organisers of this event for the tremendous effort to keep all scientific and allergy workers together. This was a virtual taste of what will be the new world of meetings!

The presentations included symposia, which were still "state-of-the-art" educational sessions, and thematic poster sessions, found in the e-poster section, were also available on the EAACI congress platform. The "year in review" was also a very attractive session type.

There were a lot of challenging topics discussed at this year's meeting: the role of microbiome, gene interactions, novel insights into the development of allergic diseases, and much more. Immunotherapy for aeroallergens and foods were widely presented with great interest. And what about the new biomarkers and novel treatment for dermatitis and asthma? Very interesting!

The pandemic situation was an opportunity to review all the concepts of inflammatory models. Naturally, the mechanisms of coronavirus disease 2019 (COVID)-19 were largely covered. With this, we will be better at prevention and treating patients in the future.

Again, this year brought me some high-quality papers for the journal. My Editor's Pick for this issue is the paper titled: "The Psychosocial Impact of Adolescent Food Allergy: A Review of the Literature" by Newman and Knibb. As the prevalence of food allergy has been increasing, there has been growing demand for psychosocial support for adolescents with food allergies. This review explores the psychosocial impact of having a food allergy. The review concludes with considerations of the wider community which may also have an impact.

Again, thanks for your loyalty to *EMJ Allergy & Immunology*. And I hope this issue will help you to enhance your knowledge and stimulate your future exchanges with peers.

Enjoy reading,

Jacques Bouchard

Université Laval, Canada, and CIUSSS Capitale-Nationale, Canada

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Congress Review

Review of the European Academy of Allergy and Clinical Immunology (EAACI) Digital Congress 2020

Location: EAACI Digital Congress 2020

Date: 6th May – 8th May 2020

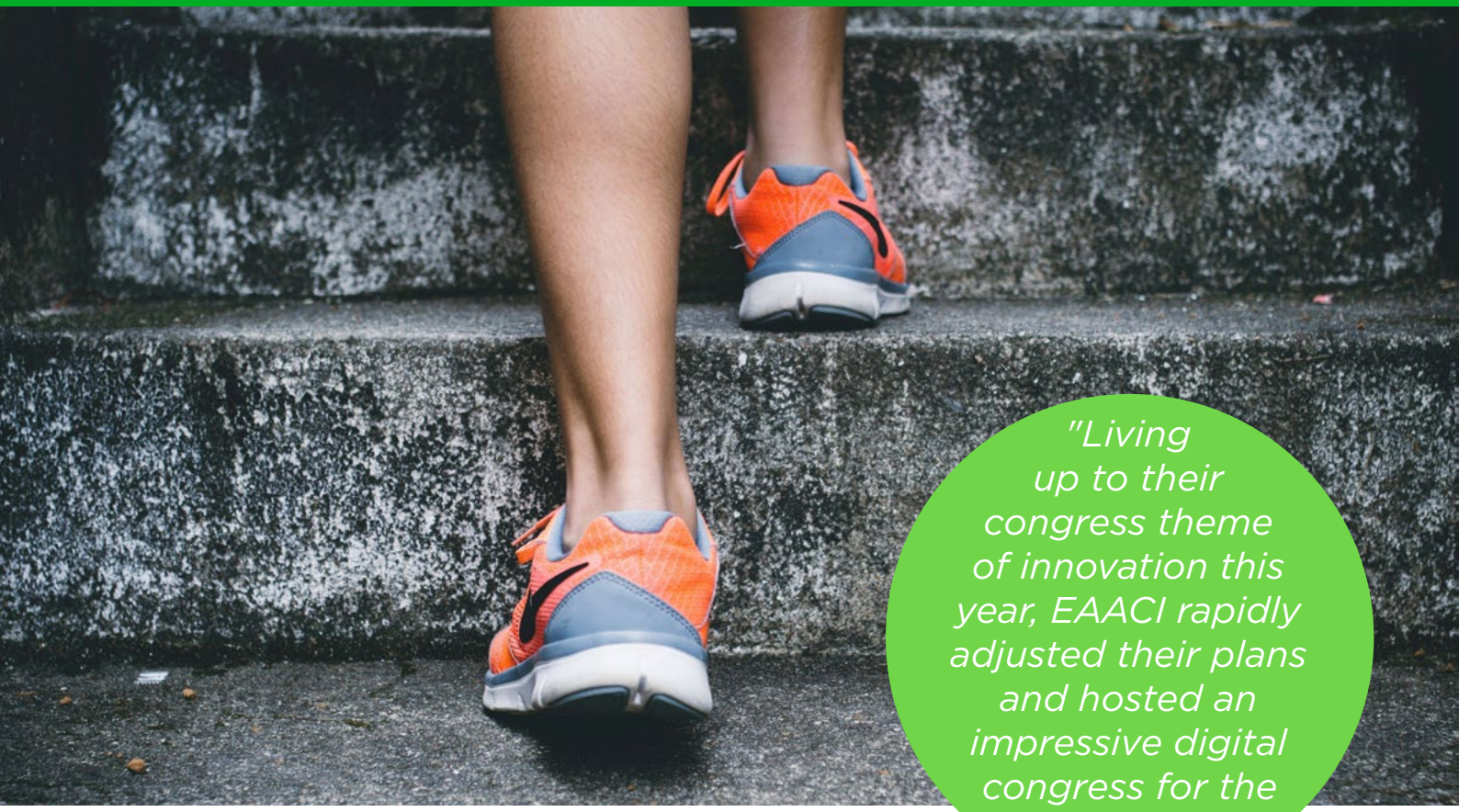
Citation: EMJ Allergy Immunol. 2020;5[1]:12-18. Congress Review.

THOUSANDS of immunologists, allergists, and clinicians involved in the research and care of allergies were due to come together in the first week of May at ExCel London, London, UK, for the annual congress of the European Academy of Allergy and Clinical Immunology (EAACI). But ExCel had been transformed into a massive intensive care unit, the National Health Service (NHS) Nightingale, and the COVID-19 pandemic meant that this allergy community had to adapt to a new digital format for their congress. Living up to their congress theme of innovation this year, EAACI rapidly adjusted their plans and hosted an impressive digital congress for the first time.

Undaunted by the challenges of their first digital congress, EAACI provided a wide array of session formats to showcase an astounding volume of research and host thoughtful discussions with experts and stakeholders. Poster sessions and abstracts were accompanied by interactive symposia, courses, and ethics, 'hot topics', year in review, and 'pro & con' sessions. Particularly engaging were many live-hosted sessions, allowing for interaction via an online chat function to facilitate the discussion that would normally occur during a face-to-face congress.

The theme of this year's congress was 'bridging innovations into allergy and asthma prevention' and EAACI President Prof Marek Jutel, Wrocław Medical University, Wrocław, Poland, highlighted the role of this theme in empowering the value of the congress: "This year's congress motto suggests that we will not only present state-of-the-art knowledge in allergy and clinical immunology but will go beyond this, bridging it with the most contemporary, inspiring, and creative processes and ideas diffused and adapted to the needs of our patients."

During the welcome message, Nobel Prize Laurate Sir Gregory P. Winter, University of Cambridge, Cambridge, UK, presented the first keynote lecture, in which he discussed



"Living up to their congress theme of innovation this year, EAACI rapidly adjusted their plans and hosted an impressive digital congress for the first time."

the history of biologicals and their place in modern medicine, adding recently learned knowledge about SARS-CoV-2. The second keynote lecture about coronavirus and their influence in lung inflammation was delivered by Prof Peter Openshaw, Imperial College London, London, UK. Finally, Prof Jutel explored the recent data on immune modulation in the era of COVID-19.

This year, Prof Santiago Quirce, Prof George du Toit, Prof Mübeccel Akdis, and Prof José María Olaguibel were respectively awarded the Clemens von Pirquet, Daniel Bovet, Paul Ehrlich, and Charles Blackley awards for their contributions to allergy and immunology. Other allergists honoured at this year's congress included Dr Rodrigo Jimenez Saiz (Allergopharma Award), Dr Paul Turner (PhARF Award), and Dr Giorgio Walter Canonica, Dr Claudia Traidl-Hoffmann, Dr Sebastian Johnston, and Dr Nikos Papadopoulos (EAACI Fellow Award).

Compelling research presented at the congress included the consideration of the role of allergy in the current COVID-19 pandemic, and in wider clinical fields; the role of air pollution in COVID-19 outcomes; bathing frequency of infants and the risk of atopic dermatitis; and proangiogenic features of B cells that may contribute to cancer and inflammation. Additionally, EAACI launched their guidelines for the use of biologic therapies in asthma at the congress.

EAACI represents over 75 national allergy societies and is made up of more than 12,000 members from 124 countries. Originally founded in 1956, EAACI has grown to become the largest medical association in Europe for the field of allergy and clinical immunology, and celebrates that it is "the primary source of expertise in Europe and worldwide for all aspects of allergy." For the first digital congress, 5,000 people attended online and built the same collaborative community expected of a face-to-face congress via online chat and Twitter. The congress tradition of a 'Beat Allergy Run' shifted online, with participants sharing their progress during the congress from their homes around the world with #VirtualBeatAllergyRun. Prof Jutel celebrated this adaptive community: "Change is not only about embracing new ideas but also about leaving outdated ones behind, and what better opportunity to do so than taking part in this completely new format of annual congress?"

EAACI DIGITAL CONGRESS 2020 REVIEWED →

Is Air Pollution Worsening the COVID-19 Pandemic?

NITROGEN dioxide, ozone, and respirable particulate matter (PM), all examples of gases than modify the permeability of airway mucosa, may render individuals more susceptible to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This was announced in a press release on 7th June 2020 at the EAACI Digital Congress 2020.

Exposure to fine PM or ultrafine carbon black particles is known to heighten respiratory virus-induced inflammation, and long-term exposure to such air pollution leads to chronic systemic inflammation. This is thought to be partially caused by a decreased ability of macrophages to phagocytise a virus and thereby produce an ineffective immune response against the infection.

This chronic immune response causes many of the comorbidities that put patients at higher risk of severe COVID-19. However, it was noted by Prof Gennaro D'Amato, University of Naples, Naples, Italy, that the virus, and indeed other respiratory diseases such as chronic obstructive pulmonary disease, could be utilising polluting particles as 'territories', whilst also surviving longer in immune environments that are already aggravated by irritants such as air pollution.

Protecting the environment could therefore be imperative in these unprecedented times, highlighted Prof D'Amato: "It is important to consider that these potential correlations can be reduced by reducing deforestation, by reducing old components that increase air pollution and climate change." These results signify the importance of this topic to all countries, and the planet.

"It is important to consider that these potential correlations can be reduced by reducing deforestation, by reducing old components that increase air pollution and climate change."

Do Proangiogenic B Cells Play a Role in Cancer and Chronic Inflammation?

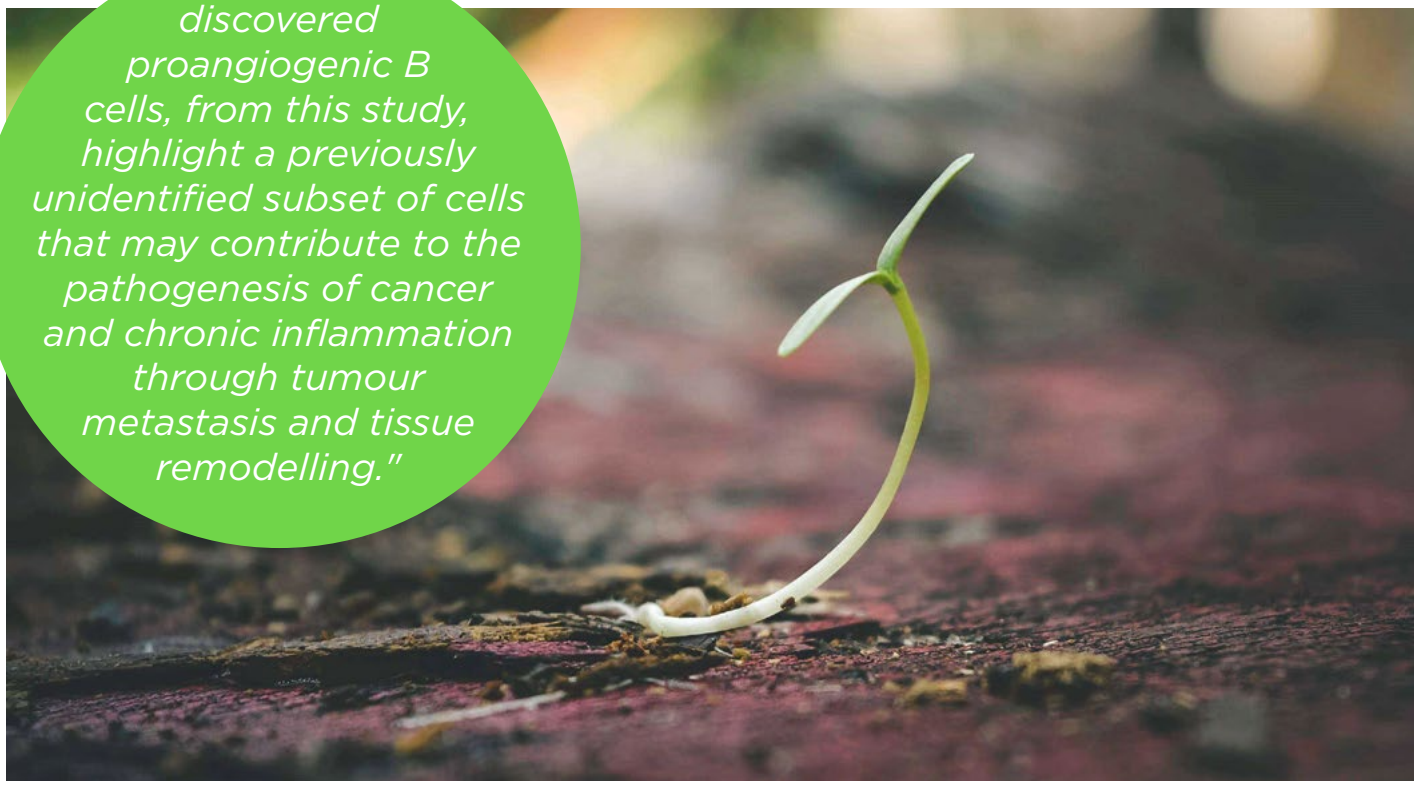
ANGIOGENESIS, the formation of new blood vessels, has been shown to play a central role in the pathogenesis of conditions including cancer metastasis and tissue remodelling in chronic inflammation. A new study presented at EAACI Digital Congress 2020 on 6th June has reported the identification of a subset of B cells with angiogenic function.

B cells are primarily known for their role in humoral immunity; however, it is becoming increasingly evident that they also have other functions mediated by the cytokines they produce, which further define the effector function of the immune cell. The process of angiogenesis is governed by a group of proangiogenic mediators including cytokines, chemokines, and growth factors. In the study lead by Dr Willem van de Veen and Prof Mübeccel Akdis, Swiss Institute of Allergy and Asthma Research (SIAF), Davos, Switzerland, a subset of B cells characterised by the production of a broad range of proangiogenic cytokines were identified. The cytokine profile of the cells strongly correlated with B cells that switched to IgG4, known for its anti-inflammatory properties. IgG4 has been reported to be associated with conditions such as melanoma and eosinophilic esophagitis, with enhanced IgG4 response against food allergens reported in the latter. The described B cells expressed increased levels of CD73 and CD49b, which catalyse the conversion of ATP to free adenosine, a known proangiogenic factor.

The proangiogenic B cells were found primarily, and at elevated levels, in the peripheral blood of patients with melanoma and eosinophilic esophagitis, diseases associated with angiogenesis. Furthermore, in these patients, tissue-infiltrating IgG4+, CD49b+, and CD73+ B cells expressing proangiogenic cytokines were also detected.

The discovered proangiogenic B cells, from this study, highlight a previously unidentified subset of cells that may contribute to the pathogenesis of cancer and chronic inflammation through tumour metastasis and tissue remodelling. Future research will aim to investigate the potential clinical strategies of targeted therapies aimed at depletion of B cells in melanoma, eosinophilic esophagitis, and other inflammatory diseases.

"The discovered proangiogenic B cells, from this study, highlight a previously unidentified subset of cells that may contribute to the pathogenesis of cancer and chronic inflammation through tumour metastasis and tissue remodelling."



Bathing Frequency Impacts the Risk of Atopic Dermatitis in Infants

Overall, the study showed that there was an association between an increase in bathing frequency in infants and an increase in TEWL and risk of AD.

BATHING of newborns varies in frequency, but according to a study by King's College London and St. George's University, both in London, UK, that was presented at EAACI Digital Congress 2020 and highlighted in a press release dated 6th June, an increased frequency of bathing during infancy is associated with an increased risk of developing atopic dermatitis (AD).

Affecting approximately 15–20% of children worldwide, AD is one of the most common inflammatory skin diseases. Symptoms of AD generally present during infancy, with 60% of patients developing them before the age of 1 year. These initial symptoms can evolve into debilitating pruritus (itchiness), sleeplessness, and a severe reduction of quality of life. In addition to established genetic links, an increased risk of AD can be associated with environmental exposures that disrupt the function of the skin barrier.

In the study, healthy infants with no known dietary or health conditions, who were full term, and were exclusively breastfed were assessed. The infants were from across Wales and England and were enrolled in the EAT randomised controlled trial. When the infants were 3 months of age, the parents completed questionnaires that asked how they care for their baby's skin. The infants' skin barrier function was measured by assessing transepidermal water loss (TEWL); additionally, the infants were examined for AD.

For each additional bath of the infant, there was an increase in TEWL. Additionally, a bathing frequency of more than once a week was associated with an increase in AD risk at 3 months; however, this was not seen at the 12-month follow-up. These results remained even after adjusting for confounding factors, such as filaggrin mutation status, water hardness, and emollient application.

Overall, the study showed that there was an association between an increase in bathing frequency in infants and an increase in TEWL and risk of AD. Further studies, in the context of an intervention study, on bathing frequency and the overall impact of skin hygiene practices have been called for.

New Guidelines for the Use of Biologicals in Patients with Severe Asthma

NOVEL guidelines for the use of biologicals in patients with severe asthma, which is a rapidly evolving field, were presented at the EAACI Digital Congress this year on 6th June 2020.

Patients, families, and healthcare professionals affected by severe asthma bear a significant burden because of the disease heterogeneity, comorbidities, challenges associated with pathways of care, and the differences in healthcare both nationally and regionally. The management of severe asthma has become well-controlled with better understanding of the disease pathogenesis. The use of biologicals for targeted treatment is supported; however, uncertainties regarding the selection of biologicals remain. Prof Marek Jutel, the President of EAACI, posed some of the key questions about the use of biologicals for the management of severe asthma: "What are the best strategies to enhance the respondent's rate? What is the optimal duration of treatment and its cost-effectiveness? And, what is the appropriate regimen, in the clinic or home-based?"

The new EAACI guidelines on the use of biologicals in severe asthma follow the GRADE approach to devise biological and asthma outcome recommendations. As well as this tool, a management algorithm for the use of biologicals, future approaches to the field, and research prospects were put forward. Prof Oscar Palomares, Biologicals Guidelines Project Co-Chair, Complutense University of Madrid, Madrid, Spain, commented on the significance of these advancements for "healthcare providers, patients, regulators, and healthcare systems providing specific recommendations for each biological in the context of each independent outcome."

Modern medicine has seen tremendous advances in the use of biologicals (namely, monoclonal antibodies); the potential that biologicals hold and the associated challenges were raised at the congress by Sir Gregory Paul Winter, special guest and 2018 Nobel Prize Winner for Biochemistry. He shared the side effects of corticosteroids, such as fluid retention, hypertension, and bone loss, and commented on the benefits of monoclonal antibodies: "Ideally, treatments should have a more specific mode of action and avoid these side effects." He commented further on the potential of biologicals: "These biologicals are of high efficiency and exquisite specificity, they have a long half-life in serum, and properties and functions can be tailored to order. Their impact has already been immense and [are] likely to become greater still." EAACI hope that the new guidelines will serve as a reference point in the field for the foreseeable future.

"These biologicals are of high efficiency and exquisite specificity, they have a long half-life in serum, and properties and functions can be tailored to order. Their impact has already been immense and [are] likely to become greater still."

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Breakthrough in the Understanding of the Anti-IgE Pathway in Chronic Spontaneous Urticaria and the Potential of Ligelizumab

This congress report is based on a virtual symposium, two oral presentations, and two poster presentations that took place between 6th and 8th June 2020, as part of the European Academy of Allergy and Clinical Immunology (EAACI) Digital Congress 2020

Speakers: Marcus Maurer,[1] Alexander Eggel,[2] Jonathan A. Bernstein,[3] Ana M. Giménez-Arnau,[4] Weily Soong[5]

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Disclosure: Prof Maurer is or recently was a speaker and/or advisor for and/or has received research funding from Allakos, Aralez, ArgenX, AstraZeneca, Celldex Therapeutics Inc, Centogene, CSL Behring, FAES, Genentech, GI Innovation, Innate Pharma, Kyowa Hakko Kirin Co., Ltd, LEO Pharma, Eli Lilly and Company, Menarini, Moxie Pharmaceutical Private Limited, Merck & Co, Novartis, Roche Holding AG, Sanofi Regeneron, Third Harmonic Bio, UCB, and J. Uriach y Compania S.A. Dr Eggel has received research support from the Swiss National Science Foundation, the Fondation Acteria, the Velux Stiftung, the Research Fund of the Swiss Lung Association (Bern), the Uniscientia foundation, the Allergie Stiftung Ulrich Müller -Gierok, the National Institutes of Health (NIH); has received travel support from Novartis and the Swiss Society for Allergology and Immunology; and is employed by the Insel Gruppe AG. Dr Bernstein reports employment full time/part time at the Bernstein Allergy Group and Clinical Research Center, University of Cincinnati College of Medicine; research grants (P.I., collaborator or consultant; pending and received grants) from Novartis, Genentech, AstraZeneca, Sanofi Regeneron, Merck & Co, Shire, CSL Behring, Biocryst Pharmaceuticals, Pharming; other research support from the National Institute of Allergy and Infectious Diseases (NIAID); speakers bureau/honoraria from Novartis, Genentech, AstraZeneca, Sanofi Regeneron, Shire, CSL Behring, Pharming; and consultant/advisory board fees from Novartis, Genentech, AstraZeneca, Sanofi Regeneron, Merck & Co, Shire, CSL Behring, Biocryst Pharmaceuticals, Pharming. Prof Giménez-Arnau has served as medical advisor for J. Uriach y Compania S.A., Genentech, Novartis, FAES, GlaxoSmithKline, Sanofi; has received research grants supported by J. Uriach y Compania S.A. and Novartis; grants from Instituto Carlos III (FEDER); and has been involved in educational activities for J. Uriach y Compania S.A., Novartis, Genentech, Menarini, LEO Pharma, GlaxoSmithKline, Merck & Co, Almirall, and Sanofi. Dr Soong has been an advisor and/or clinical investigator, received consulting fee(s), and/or grant(s) for/from AbbVie, Aimmune Therapeutics, AstraZeneca, Cara Therapeutics, Galderma, Genentech, GlaxoSmithKline, Stallergenes Greer, OptiNose AS, Glenmark Pharmaceuticals, Gossamer Bio, Vanda Pharmaceuticals Inc., Relaxar Therapeutics Inc., Avillion LLP, Menlo Therapeutics, Novartis, Pfizer, Regeneron, Sanofi, and Teva Pharmaceutical Industries Ltd.

Acknowledgement: Writing assistance was provided by Jenny Lloyd, Compass Medical Communications, Ltd., Kent, UK.

Support: The publication of this article was funded by Novartis. The views and opinions expressed are those of the authors and not necessarily those of Novartis.

Citation: EMJ Allergy Immunol. 2020;5[1]:20-27.

Meeting Summary

A virtual symposium at the European Academy of Allergy and Clinical Immunology (EAACI) Digital Congress 2020 addressed breakthroughs in the understanding of the role of the IgE pathway in the inflammatory process, which leads to chronic spontaneous urticaria (CSU) symptoms, and discussed treatments that target this pathway. Two anti-IgE antibodies (omalizumab and ligelizumab) have distinct molecular properties and modes of action. Ligelizumab has an approximately 90-fold higher affinity for IgE than omalizumab, and inhibits the IgE/FcεRI pathway, which plays an important role in CSU. Adding to data presented during the symposium, several presentations throughout the congress reported data from a Phase IIb study and/or its extension. In this study, patients with moderate/severe CSU were randomised to receive ligelizumab 24, 72, 240 mg; omalizumab 300 mg; or placebo every 4 weeks (q4w) for 20 weeks. Complete hive control (weekly Hives Severity Score [HSS7]=0) was achieved by 30.2%, 44.0%, 51.2%, 42.4%, and 0.0% of patients, respectively, at 12 weeks. In severe CSU, weekly Urticaria Activity Score (UAS7=0) was achieved by 38.1% and 41.1% of patients on ligelizumab 72 and 240 mg, respectively, versus 20.0% on omalizumab 300 mg, increasing to 60.0% and 40.7% versus 34.4%, respectively, in moderate CSU. Among patients with baseline angioedema, those on ligelizumab achieved rapid and sustained weekly Angioedema Activity Score (AAS7), UAS7, and Dermatology Life Quality Index (DLQI) score improvements. Among patients who received omalizumab 300 mg in the core study followed by ligelizumab 240 mg in the 1-year extension, 30.2% achieved UAS7=0 after 12 weeks of omalizumab, but 43.4% achieved UAS7=0 after 12 weeks of ligelizumab. Lastly, the median time to loss of UAS7=0 during a treatment-free period after the core study was longest after ligelizumab 240 mg (10.5 weeks). Median time to loss of UAS7≤6 was also longest after ligelizumab 240 mg: 14.0 and 21.0 weeks after the core and extension, respectively. Ligelizumab is currently undergoing further investigation in Phase III studies.

Introduction

CSU is the sudden, spontaneous appearance of itchy wheals (hives), angioedema, or both in the absence of specific external stimuli, for >6 weeks.[1] Worldwide, the prevalence of this debilitating disease is approximately 0.5–1.0%.[2-4] CSU is associated with a significant burden, not only on the patients (in terms of daily activities, functioning, emotional and psychological distress, loss of energy, and disturbed sleep), but also on society (with impacts including loss of productivity, absence from work, and direct and indirect healthcare costs).[2]

Current Treatment Options

The overall goal of CSU treatment is to "treat the disease until it is gone,"[1] which is crucial for patient quality of life.[5] However, CSU can be difficult to treat, which is frustrating for both patients and physicians.[6] The therapeutic approach can involve identifying and eliminating eliciting factors, and pharmacological treatment directed at mast cells and mast cell mediators.[1]

The recommended first- and second-line therapy for CSU is a standard-dosed and updosed second-generation, nonsedating H_1-antihistamine, respectively.[1] However, this fails to control symptoms in >50% of CSU patients.[2,7] Although updosing of H_1-antihistamines

improves treatment responses,[1] many patients remain symptomatic.[8] After failure of H_1-antihistamines, the third-line treatment option is to target IgE with omalizumab;[1,9] however, complete symptom control is not achieved in >50% of CSU patients even after 12 weeks of treatment with omalizumab 300 mg.[10]

Aetiology

CSU symptoms occur because of mast cell activation and the release of proinflammatory mediators (e.g., histamine).[11] There are two types of autoimmunity that drive the pathogenesis of CSU.[11] In patients with Type I autoimmune CSU (autoallergy), autoimmunity is IgE-driven, with IgE autoantibodies that bind to mast cells. When the autoallergen is bound by this IgE, there is cross-linking of IgE receptors.[11] Type IIb autoimmunity is characterised by IgG or IgM autoantibodies that are directed to the mast cell itself, with either the IgE receptor on mast cells or the IgE bound to them.[11] Both types result in downstream mast cell activation or degranulation and hives and/or angioedema.

IgE binds to two main receptors: high-affinity FcεRI receptors and low-affinity CD23 (FcεRII) receptors.[12] The resultant IgE cross-linking leads to cell activation and degranulation.[12,13] The released proinflammatory and vasoactive mediators result in the clinical manifestations of CSU. This can also be triggered directly by autoantibodies attaching to the FcεRI receptors. Either way, the IgE receptor is key to mast cell activation in CSU.[13,14] Therefore, an anti-IgE drug that prevents mast cell activation reduces the symptoms of CSU.

Anti-IgE Antibodies

As the IgE/Fcε RI axis plays a central role in allergen and autoantigen-driven inflammation in CSU, the goal of the anti-IgE approach is to bind and neutralise free IgE in a patient's serum.[15] The anti-IgE antibodies thus block the binding of IgE to the high-affinity receptors on mast cells and basophils, resulting in reduced hypersensitivity reactions and fewer CSU symptoms (hives, itching, and angioedema).

Two anti-IgE antibodies have shown efficacy in CSU: omalizumab, which is currently licensed for the treatment of CSU; and ligelizumab, which is a next-generation, high-affinity, humanised monoclonal anti-IgE antibody that is currently in development for the treatment of patients with CSU who are inadequately controlled by an H_1-antihistamine.[16] These two antibodies have distinct molecular properties and modes of action, as discussed in this article.

In a Phase I double-blind study, atopic subjects were randomised to receive 2–4 doses of subcutaneous ligelizumab 0.2, 0.6, 2.0, or 4.0 mg/kg or placebo every 2 weeks, and the results were compared with an open-label omalizumab arm.[17] At a dose of 4.0 mg/kg, ligelizumab reduced the amount of free IgE to a much greater extent than omalizumab, and the reduction persisted for considerably longer.[17] There was a concomitant rapid increase in total IgE with ligelizumab because of the formation of stable complexes between IgE and ligelizumab, and this persisted for longer than with omalizumab.[17]

A recent binding study has shown that ligelizumab has an approximately 90-fold higher affinity for IgE than omalizumab.[15] This is partly because of the higher association constant of ligelizumab's antigen-binding fragment compared to omalizumab's antigen-binding fragment (9.2×10^6 versus 1.5×10^6 $M^{-1}s^{-1}$, respectively), but mainly because of the much lower dissociation constant (3.2×10^{-4} versus 4.6×10^{-3} s^{-1}, respectively), resulting in a considerably lower equilibrium dissociation constant (35 versus 3090 pM, respectively).[15] This likely explains the more stable complex seen in the previous study.

By examining the crystal structures of complexes between IgE and either ligelizumab or omalizumab, it has been shown that ligelizumab binds to a different IgE epitope than omalizumab.[15] Although both antibodies bind in the same IgG domain (Cε3), ligelizumab binds more proximally to the Cε2 domain and has an important overlap with the binding site for the high-affinity FcεRI receptor.[15] In contrast, omalizumab binds closer to the Cε4 domain, i.e., further from the FcεRI site, instead directly competing with the low-affinity CD23 receptor.[15] Of note, ligelizumab can bind to IgE that is already bound to CD23, but not IgE that is bound to FcεRI.[15] Lastly, ligelizumab preferentially binds to

an open conformation of IgE, in a similar way to when it binds to the high-affinity receptor.[15] These data predict better inhibition of an interaction between IgE and FcεRI with ligelizumab, and better inhibition of an interaction between IgE and CD23 with omalizumab, and this has been confirmed in functional assays.[15] Because of its stronger inhibition of IgE binding to FcεRI, ligelizumab is predicted to be more effective than omalizumab in CSU.

Ligelizumab also suppresses the production of IgE by B cells (in peripheral blood mononuclear cells stimulated with anti-CD40 and IL-4) to a greater extent than omalizumab,[15] which could further explain the prolonged suppression of free IgE in patients receiving ligelizumab.

Overall, omalizumab is more efficient at suppressing CD23-related pathways, which are heavily involved in allergic asthma, while ligelizumab is more efficient in FcεRI-mediated pathways, which are heavily involved in CSU and food allergies.

Phase IIb Ligelizumab Study

Study Design and Patient Disposition

In a key Phase IIb, randomised, double-blind, dose-finding study of ligelizumab for CSU,[18] following a 2-week screening period, 382 adult patients with moderate-to-severe CSU (UAS7≥16 on a scale of 0–42, with higher scores indicating more severe disease) that was inadequately controlled with an H_1-antihistamine were randomised to recieve:[16]

- Ligelizumab 24 mg q4w (n=43)
- Ligelizumab 72 mg q4w (n=84)
- Ligelizumab 240 mg q4w (n=85)
- Omalizumab 300 mg q4w (n=85)
- Placebo q4w (n=43)
- One dose of ligelizumab 120 mg followed by placebo q4w (n=42) (for pharmacokinetic/pharmacodynamic characterisation).

The treatment phase lasted until Week 20, with treatments given subcutaneously at Weeks 0, 4, 8, 12, and 16, after which patients were followed up to Week 32–44 without treatment. From Week 32, patients could enrol in a 1-year extension study[19] on ligelizumab 240 mg q4w if their UAS7 was ≥12. They were then followed up for a further year without treatment to assess the durability of the treatment effect. Of the 226 patients who entered the extension study, 201 completed this open-label phase.

Core Study Results

At Week 12, HSS7=0 (primary outcome measure) had been achieved by 30.2%, 51.2%, and 42.4% of patients on ligelizumab 24, 72, and 240 mg, respectively, compared with 25.9% of those on omalizumab and no patients in the placebo arm.[16] Similarly, UAS7=0 at Week 12 was achieved by 30.2%, 44.0%, and 40.0% of patients on ligelizumab 24, 72, and 240 mg, respectively, compared with 25.9% of patients on omalizumab and no patients in the placebo arm.[16] Mean changes in UAS7 scores from baseline to Week 12 were -16.5 with ligelizumab 24 mg, and -22.0 and -21.8 with ligelizumab 72 and 240 mg, respectively, compared with -17.9 with omalizumab and -13.4 with placebo.[20]

In an exploratory analysis, which included the ligelizumab 72 and 240 mg groups and the omalizumab group, efficacy results were examined according to baseline CSU activity. CSU disease activity was categorised into five groups based on UAS7 scores: 0 (urticaria free), 1–6 (low activity), 7–15 (mild), 16–27 (moderate), and 28–42 (severe). At baseline, most patients had severe CSU activity (58.8–75.0% in the three reported treatment groups) or moderate CSU activity (23.8–37.6%). Among those with moderate CSU activity at baseline, a complete response (UAS7=0) was achieved by Week 4 in 35.0% and 25.9% of patients on ligelizumab 72 and 240 mg, respectively, compared with 12.5% of patients on omalizumab. A further 35.0% (ligelizumab 72 mg), 22.2% (ligelizumab 240 mg), and 21.9% (omalizumab) of patients achieved UAS7 1–6. Achievement of UAS7=0 increased to 60.0% (ligelizumab 72 mg), 40.7% (ligelizumab 240 mg), and 34.4% (omalizumab) of patients by Week 12; a further 20.0% (ligelizumab 72 mg), 14.8% (ligelizumab 240 mg), and 25.0% (omalizumab) of patients achieved UAS7 1–6. Up to 90% of patients decreased by ≥1 activity level, and up to 70% and 80% of ligelizumab-

treatment patients at Week 4 and Week 12, respectively, were considered well controlled. Among those with severe CSU activity, most patients achieved improvements in UAS7 scores, with 38.1% (ligelizumab 72 mg), 41.1% (ligelizumab 240 mg), and 20.0% (omalizumab) achieving UAS7=0 by Week 12 (Figure 1). Up to 70% of patients improved by ≥1 activity band.

Quality of Life Outcomes

Quality of life outcomes were studied amongst a subgroup of CSU patients with angioedema at baseline (ligelizumab 72 mg [n=43], ligelizumab 240 mg [n=46], omalizumab 300 mg [n=48], or placebo [n=28]). Patients in the two ligelizumab groups achieved dramatic and sustained improvements in UAS7 as early as Week 4 (i.e., after just one dose): baseline → Week 4 → Week 12 → Week 20 mean UAS7 were 33 → 12 → 10 → 9 with ligelizumab 72 mg and 30 → 13 → 9 → 7, respectively, with ligelizumab 240 mg. Scores also improved in the omalizumab group, but to a somewhat lesser extent (30 → 16 → 13 → 11, respectively). Patients in the placebo group also experienced some improvement (32 → 26 → 17 → 16, respectively), caused by spontaneous resolution of symptoms. Improvements in mean AAS7 followed a generally similar pattern, with those in the ligelizumab 72 mg (42 → 8 → 6 → 6, respectively) and ligelizumab 240 mg (33 → 12 → 7 → 5, respectively) groups achieving large, rapid reductions in AAS7, with similar results in the omalizumab group (31 → 12 → 7 → 4, respectively), and a smaller spontaneous improvement in the placebo group (40 → 22 → 14 → 14, respectively). Mean DLQI scores at baseline were approximately 15 in each of the four groups. At Week 4, these had decreased to 5 (ligelizumab 72 mg), 6 (ligelizumab 240 mg), 7 (omalizumab), and 11 (placebo). At Week 12, mean DLQI scores were 4–6 in all four groups, and at Week 20, the mean DLQI score in the ligelizumab 240 mg group was 3, compared to 6–7 in the other three groups. Therefore, the decreases in the UAS7 and AAS7 that were observed over time in each treatment arm were accompanied by improvements in DLQI.

Pearson correlation coefficients (r-values) for UAS7 and AAS7 with DLQI were calculated for each treatment group, using pooled data from baseline to Week 20. Significant correlations between UAS7 and DLQI were observed in each treatment arm, with r-values of 0.85 (ligelizumab 72 mg), 0.81 (ligelizumab 240 mg), 0.78 (omalizumab), and 0.69 (placebo) (all $p<0.001$), indicating stronger correlations in the ligelizumab groups. Similarly, r-values for the correlations between AAS7 and DLQI were 0.66 (ligelizumab 72 mg), 0.66 (ligelizumab 240 mg), 0.59 (omalizumab), and 0.52 (placebo) (all $p<0.001$). These results indicate that a reduction in symptoms (itch, hives, and angioedema) based on effective treatment correlates with an improvement in quality of life, and therefore wellbeing.

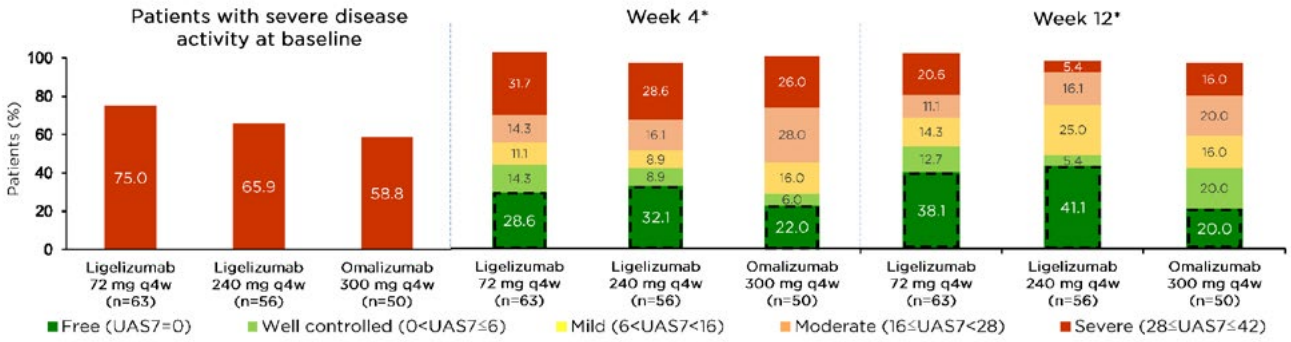

Figure 1: Among patients with severe chronic spontaneous urticaria, more ligelizumab- than omalizumab-treated patients achieved a complete response.

*The percentages do not add up to 100% as some subjects discontinued the study early or data from their visit were missing.

q4w: every 4 weeks; UAS7: weekly Urticaria Activity Score.

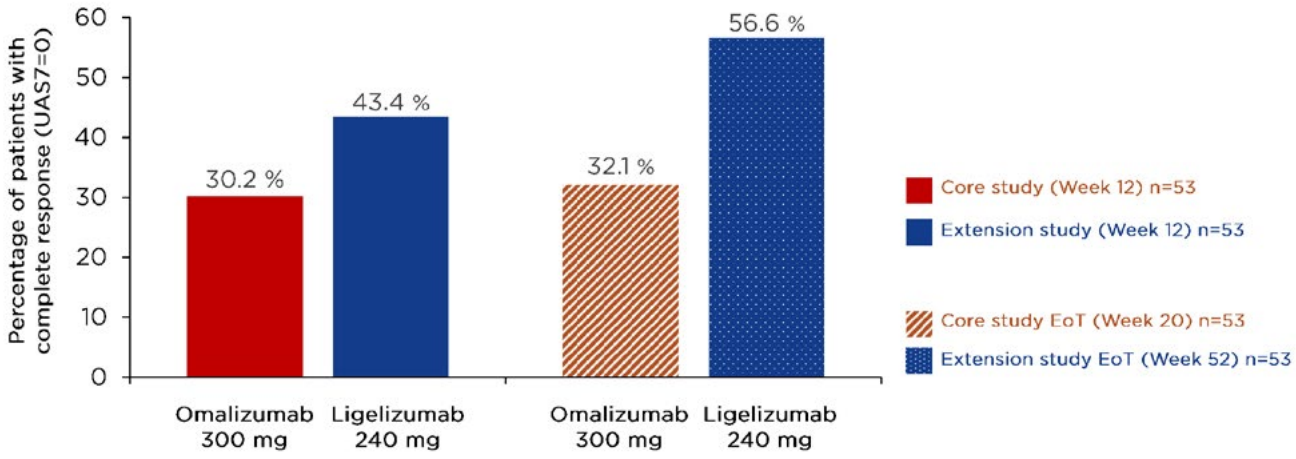

Figure 2: Patients who received omalizumab 300 mg during the core study followed by ligelizumab 240 mg in the extension study were more likely to achieve a complete response on ligelizumab.

EoT: end of treatment; q4w: every 4 weeks; UAS7: weekly Urticaria Activity Score.

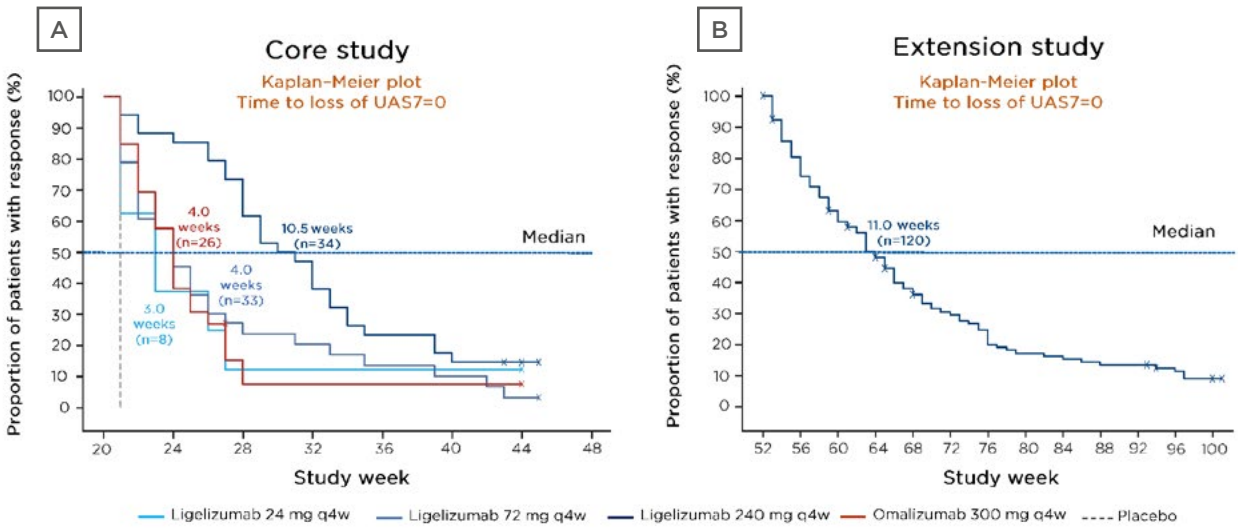

Figure 3: Kaplan–Meier plots of the times to loss of weekly Urticaria Activity Score (UAS7=0) during the treatment-free follow-up periods after the two treatment periods.

A) The 20-week core study and **B)** the 1-year extension study.[23]

X indicates censored patients who left the study without an observed loss of response.

q4w: every 4 weeks; UAS7=0: weekly Urticaria Activity Score.

Extension Study Results

Four weeks after the first dose of ligelizumab 240 mg in the 1-year extension study, 35.4% of patients had achieved UAS7=0,[21] which increased steadily to 53.1% after 1 year of treatment.[22] Similarly, 54.4% achieved UAS7≤6 (i.e., mild disease) after one dose, increasing to 61.1% after 1 year.[22]

At the start of the 1-year extension study, 33.2% of patients had angioedema, which fell to 10.8% by Week 4 and 7.0% by Week 52.[21] Mean changes from baseline in AAS7 (on a scale of 0–105, with higher scores indicating higher severity) increased from -23.2±23.7 at Week 4 (equating to a 71.9% reduction from baseline) and from -27.4±24.6 at Week 52 (equating to an 86.3% reduction from baseline).[22]

There were some interesting results among the 53 patients who received omalizumab 300 mg in the core study and then went on to receive ligelizumab 240 mg in the extension study. After 12 weeks of omalizumab 300 mg treatment in the core study, 30.2% of these 53 patients had achieved UAS7=0, and this increased slightly to 32.1% after 20 weeks. However, after 12 weeks of ligelizumab 240 mg in the extension study, 43.4% of these same patients achieved UAS7=0, increasing to 56.6% after 52 weeks (Figure 2). Therefore, while the core study demonstrated greater improvements with ligelizumab than omalizumab in a parallel-group design, the extension study results showed that patients who received omalizumab followed by ligelizumab were more likely to achieve a complete response with ligelizumab.

Post-Treatment Follow-Up Results

There were two treatment-free follow-up periods, which occurred between the 20-week core study and the 1-year extension study (n=349), and during the 1-year treatment-free follow-up after the 1-year extension study (n=201). The Kaplan–Meier median method was used to calculate the median times to: a) loss of complete control (UAS7=0) for each treatment group after the core study, and after the 1-year treatment period of the extension study; b) loss of well-controlled urticaria activity (UAS7≤6) after the core and extension studies; and c) relapse (UAS7≥16) during the follow-up period after the 1-year extension study.

After the end of the double-blind treatment period in the core study (Week 20), the median time to loss of completely controlled CSU (UAS7=0) was longest amongst the 34 patients who had achieved complete control on ligelizumab 240 mg (10.5 weeks) (Figure 3A). So, after stopping treatment at the end of the 20-week core study, it took 10.5 weeks for 50% of the patients on ligelizumab 240 mg who achieved UAS7=0 to lose this control. Median time to loss of complete control was similar amongst patients who had achieved complete control on ligelizumab 72 mg (4.0 weeks), ligelizumab 24 mg (3.0 weeks), and omalizumab (4.0 weeks) (Figure 3A).[23]

During the treatment-free follow-up period after the 1-year extension study, in which all patients received ligelizumab 240 mg, the median time to loss of UAS7=0 was 11.0 weeks amongst the 120 patients who had achieved this (Figure 3B).[23]

Similarly, the median time to loss of well-controlled CSU (UAS7≤6) was longest amongst the 38 patients who had achieved this control on ligelizumab 240 mg (14.0 weeks), followed by 7.0 weeks amongst those on ligelizumab 72 mg (n=51) or omalizumab (n=36), and 4.0 weeks for ligelizumab 24 mg (n=17).[23] After the end of the 1-year extension study (ligelizumab 240 mg), the median time to loss of UAS7≤6 was even longer (21.0 weeks) (n=138).[23]

The median time to relapse (UAS7≥16) amongst patients whose symptoms were previously well controlled (UAS7≤6) at the end of ligelizumab 240 mg treatment during the 1-year extension study was 38.0 weeks (n=138).[23]

Safety

All tested ligelizumab doses were well tolerated, with a safety profile that was comparable to those of omalizumab and placebo.[24] In the core study, in all treatment groups combined, adverse events were predominantly mild (39.8%) or moderate (30.6%).[24] Severe adverse events were less frequent in the ligelizumab groups (3.5–9.3%) than with placebo (16.3%).[24] Serious adverse events were reported by 7.0%, 2.4%, and 2.4% of patients on ligelizumab 24, 72, and 240 mg, respectively; 3.5% of those on omalizumab; and 9.3% of those on placebo in the core study, as well as 5.8% of patients on ligelizumab 240 mg in the extension study.[25] Adverse events only led to treatment discontinuation in 0.0%, 1.2%, and 1.2% of patients on ligelizumab 24, 72, and 240 mg, respectively; 2.4% of those on omalizumab; and 4.7% of placebo patients in the core study, as well as 3.5% of patients on ligelizumab 240 mg in the extension study.[25]

Conclusion

The efficacy and safety of omalizumab are well established,[26] and it is the third-line treatment option in international guidelines.[1] However, ligelizumab is more effective at inhibiting the IgE/FcεRI pathway than omalizumab, has a higher

affinity to IgE, and results in deeper suppression of IgE.[15] Phase IIb data indicate that patients can achieve greater symptom improvements with ligelizumab versus omalizumab, when compared in a parallel-group design and when patients who received omalizumab subsequently received ligelizumab. Ongoing Phase III ligelizumab clinical trials include PEARL 1[27] and PEARL 2,[28] in which patients inadequately controlled with H_1-antihistamines are being randomised to ligelizumab, omalizumab, or placebo; and an open-label extension study.[29] These will evaluate the efficacy and safety of ligelizumab treatment for up to 1 year in patients with CSU that is inadequately controlled with H_1-antihistamines at approved doses. Although ligelizumab is not yet approved for use, it is hoped that these new ligelizumab data may impact upon the CSU guidance algorithms in the future.

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New Advances in the Prevention and Management of Food Allergy

This symposium took place on 7th June 2020, as part of the European Academy of Allergy and Clinical Immunology (EAACI) Digital Congress 2020

Chairperson: Yvan Vandenplas[1]

Speakers: Carina Venter,[2] Norbert Sprenger,[3] Anna Nowak-Wegrzyn[4]

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Disclosure: Dr Venter has provided and reviewed education material for Danone, Abbott, Reckitt Benckiser Group plc, and DBV technologies; provided research support to Reckitt Benckiser Group plc; and received speaker honorarium from Nestlé Health Science S.A. Dr Sprenger is an employee of Société des Produits Nestlé S.A., at the Nestlé Institute of Health Sciences S.A. Prof Nowak-Wegrzyn has received honorarium from Nestlé Health Science S.A. for this presentation as well as a research grant for the clinical study of whey-based extensively hydrolysed formula with two human milk oligosaccharides, for which she was principal investigator.

Acknowledgements: Medical writing assistance was provided by Jennie James, Surrey, UK.

Support: The publication of this article was funded by Nestlé Health Science. The views and opinions expressed are those of the speakers.

Citation: EMJ Allergy Immunol. 2020;5[1]:28-36.

Meeting Summary

This symposium explored the role of nutritional interventions relating to food allergy, first in terms of prevention strategies and then management, focussing on the benefits of human milk oligosaccharides (HMO) in the management of cow's milk protein allergy (CMPA). The first speaker, Dr Venter, discussed the benefits of introducing allergenic foods at the time of commencing complementary feeding to prevent future food allergies. She summarised current guidelines on food allergy prevention, which are all in agreement that there is no reason to withhold or delay the introduction of allergenic foods in infancy, and discussed the logistics of food allergen introduction in the first year of life. The talk ended with promising research associating a diverse diet in infancy with reduced risk of food allergy over early and late childhood. Next, Dr Sprenger described how HMO, a major component of breast milk, play an important role in supporting the immune system of infants. He shared evidence suggesting that specific HMO protect breastfed infants from infections as well as clinical findings showing that the addition of two common HMO to regular infant formula helps protect healthy infants from lower respiratory tract infections (LRTI) and related antibiotic use, likely in part through their effects on the gut microbiome of young infants. Prof Nowak-Wegrzyn then reviewed the latest trial data showing that the addition of two HMO to hypoallergenic formula also reduced the risk of respiratory tract infections in infants with CMPA.

How to Implement Nutritional Strategies for Food Allergy Prevention

Doctor Carina Venter

Guidelines for the prevention of food allergy have evolved significantly over the last two decades. The definition of an infant at high risk of food allergy has shifted from being based on a familial risk of allergic diseases to an infant's own risk of developing food allergy; infants at higher risk include those with eczema and/or an existing food allergy (egg allergy in particular is considered to be a risk factor for the development of peanut allergy). Advice for families to avoid peanut and/or other food allergens during pregnancy, breastfeeding, and the infant's first few years of life has also been abandoned in light of accumulating evidence that early food allergen introduction can be beneficial for the prevention of future food allergies.[1]

In the last few years, guidance on when to introduce food allergens into the infant diet has been developed. This followed the publication of a number of studies, in particular the LEAP and EAT studies which suggested or recommended no need to delay active introduction of food allergens, particularly peanut and egg, in the infant's first year of life. The guidance related to both infants at higher risk and those in the general population.[2,3]

A summary of current guidelines showed that the practical approach is to introduce food allergens when the infant is developmentally ready to eat and once the infant has consumed a few foods. Dr Venter explained this is irrespective of the infant's risk of developing food allergies because until it is possible to clearly define 'high risk', it is perhaps sensible to treat all infants the same. This practical approach is validated by scientific opinions from both the United States Department of Agriculture (USDA) and the European Food Safety Authority (EFSA), which recommend introduction of solid foods once the infant is developmentally ready.[4,5] Both suggest introducing peanut and cooked egg in early infancy for the prevention of peanut and egg allergy, respectively.

There are practical dilemmas for food allergen introduction, such as the appropriate dose to give and the development of suitable food formats for young infants. Randomised controlled trial outcomes provide some guidance on dose, duration, frequency, and format, but currently there is only clear data about peanut introduction and limited data about egg introduction. Guidance published by the National Institute of Allergy and Infectious Diseases (NIAID) recommends about 1–2 teaspoons of an infant-safe form of peanut, such as peanut flour or thinned peanut butter, served 1–3 times a week.[6] With regard to egg, it should be cooked according to the EAT and PETIT studies,[3,7] but what constitutes a well-cooked egg is debated, although it does include boiled and scrambled egg if it has been heated until no visible liquid remains. The dose recommended for prevention of egg allergy is also debated, but 1–2 tablespoons of well-cooked egg 1–2 times per week is in line with healthy eating guidance.[1]

In terms of introducing other major allergens for allergy prevention, there is either limited or no data and so current guidance on intake of these allergens comes from healthy eating guidelines. Dr Venter suggested that even when the data is lacking there is probably still no need to delay the introduction of the allergen, which can form part of normal dietary intake according to family practices.

Diet Diversity for Allergy Prevention

There is also promising research on diet diversity for prevention of food allergy outcomes. Diet diversity can be defined as the number of different foods or food groups consumed over a given reference period.[8] To understand the role of diet diversity on allergy outcomes, the European Academy of Allergy and Clinical Immunology (EAACI) brought together a task force that performed a systematic search of the literature (the results of which have been published in a EAACI position paper on diet diversity in pregnancy, infancy, and childhood) and found only one study that focussed on the potential association of diet diversity and development of food allergy.[9] This showed that children with a more diverse diet during the first year of life had a lower prevalence of doctor-diagnosed food allergy up until 6 years of age.[10]

Since then, a new study led by Dr Venter exploring the association between four different measures of diet diversity during infancy and development

of food allergy over the first 10 years of life has been published.[11] Dr Venter discussed results of two of the measures, focussing on the number of foods introduced over the first 9 months of life and the number of food allergens introduced over the first 12 months. Multivariate analysis showed food diversity at 6 months (p=0.0111) and food allergen diversity at 12 months (p=0.0005) significantly reduced the odds of food allergy over the first 10 years of life (Figure 1A and 1B, respectively).[11]

The exposure of the gastrointestinal microbiota to diverse foods and nutrients is a plausible mechanism for how diet diversity may affect food allergy outcomes in an infant or child. There are no published data looking directly at how infant diet diversity influences infant microbial diversity. However, increases in family food intake in the first year of life significantly increases the microbial diversity in the infant gut,[12] and can potentially be used as a measure of diet diversity. Laursen et el.[12] showed that the composition of the complementary diet was a major determinant of gut microbiota development; in particular, the transition to family foods with higher protein and fibre content in the first year of life correlated with increased gut microbiota diversity.

Furthermore, a study by Roduit et al.[13] showed that infants with a higher consumption of fish, fruit, vegetables, and yoghurt in the first year of life had increased levels of short-chain fatty acids (SCFA), such as butyrate, in faecal samples. Children with the highest levels of butyrate at 1 year of age were less likely to have a reported diagnosis of food allergy up until 6 years of age.[13] SCFA are produced by microbes in the gut and have been shown to have immune regulatory properties in animal studies. As butyrate production increases there is an upregulation of T regulatory cells, which play a key role in sustaining immune tolerance to allergens. According to Dr Venter, these data, together with evidence that increased diet diversity in the first year of life was associated with reduced food allergy outcomes up until 6 years of age, indicate that the microbiome is a plausible mechanism for tolerance induction in infants.

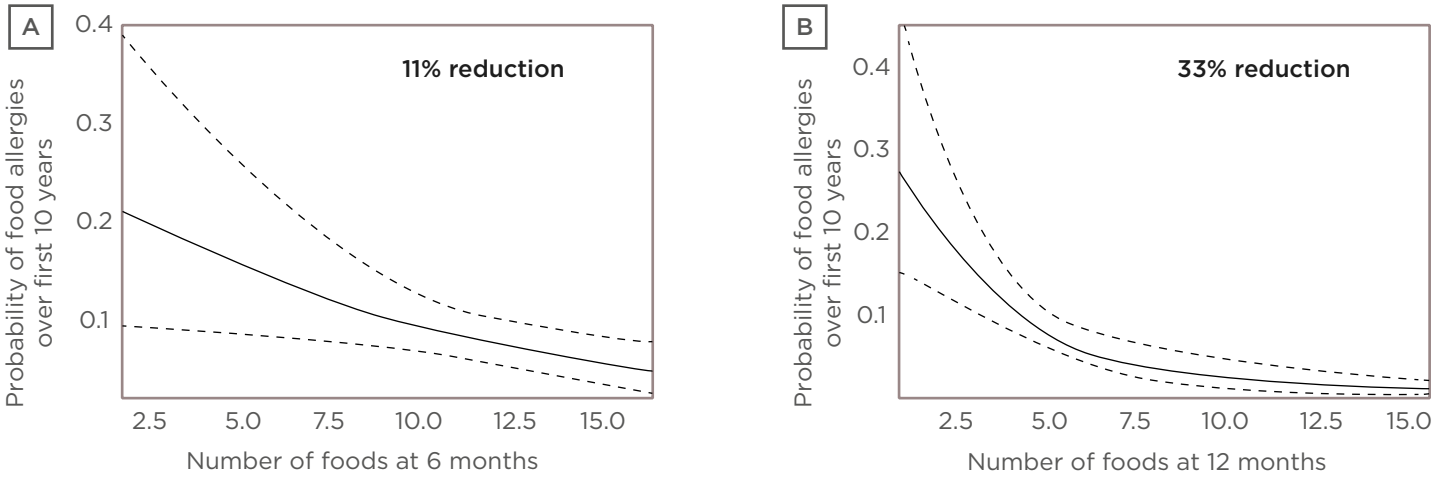


Figure 1: A) Food diversity at 6 months versus food allergy over 10 years. Multivariate analysis showed that food diversity at 6 months (p=0.0111) significantly reduced the odds of food allergy over the first 10 years of life (holding introduction of solids at the mean and ever having eczema: yes).[11] B) Food allergen diversity at 12 months versus food allergy over 10 years. Multivariate analysis showed that food allergen diversity at 12 months (p=0.0005) significantly reduced the odds of food allergy over the first 10 years of life (holding introduction of solids at the mean and ever having eczema ever: yes).

Dotted line: 95% confidence interval; solid line: p value.[11]

Human Milk Oligosaccharides for Immune System Development

Doctor Norbert Sprenger

Breast milk has a unique composition and contains many immunomodulatory components including HMO, which are the third most abundant solid component after lactose and lipids.[14,15]

These complex glycans contain a lactose core that is elongated by one or more of the monosaccharides galactose, N-acetylglucosamine, fucose, and sialic acid. HMO are structurally diverse but can be divided into three main classes: core structures, fucosylated HMO (the most common), and sialylated HMO.[15] Dr Sprenger explained that structurally, HMO resemble host intestinal epithelial glycans and differ from classical prebiotics, such as galactooligosaccharides and fructooligosaccharides, indicating that they have specific functions that cannot simply be mimicked by other 'classical' prebiotics. Two common HMO, 2'-fucosyllactose (2'-FL) and lacto-N-neotetraose (LNnT), have so far been the main focus of basic research and clinical studies into the effects of HMO in infants.

Research suggests HMO support the development of the immune system via several major functions.[16-22] These include direct effects, namely preventing pathogen growth and adhesion, reducing inflammatory responses, and aiding the mucosal barrier function, and indirect effects on the microbiota through colonisation resistance and education of the developing immune system.

HMO provide substrates for the developing gut microbiome of young infants, stimulating the growth of bifidobacteria. Several studies associate specific fucosylated HMO with bifidobacteria-dominated early-life microbiota in breastfed infants.[23-25] Studies have identified select bifidobacteria strains commonly found in breast milk, including *Bifidobacterium longum*, which can use HMO as a growth substrate. They do this by either consuming the HMO entirely (internalisation) or nibbling off the end products, such as fucose and sialic acid, which are then either internalised or left to crossfeed other microbes (extracellular breakdown).[26-29]

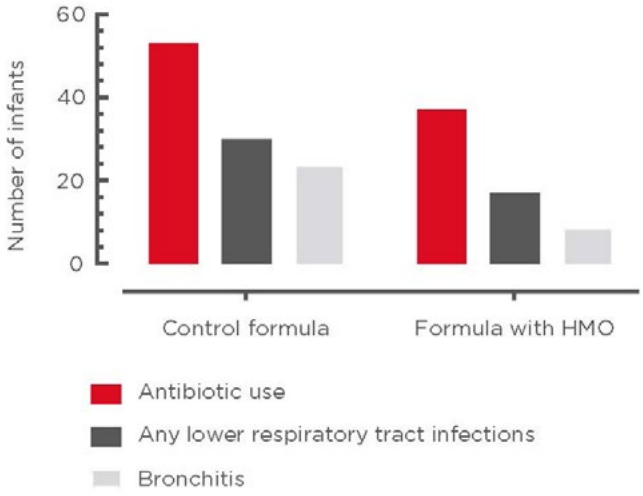
Specific HMO, including 2'-FL, not only boost the growth of bifidobacteria, but also the metabolic activity of specific bifidobacteria related to immune protection, primarily as higher formation of the SCFA acetate. This results in improved gut-barrier function and has other broader anti-inflammatory effects.[25] HMO also directly reduce microbial infections by serving as antiadhesive antimicrobials. Because HMO resemble mucosal glycans, they can act as decoy receptors for pathogens, such as *Campylobacter jejuni*, that would otherwise interact with mucosal glycans to invade the host and cause disease.[16,17]

Specific Human Milk Oligosaccharides Support the Immune System

Clinical observational studies in breastfed infants have associated breast milk containing 2'-FL, and related 2'-FL-HMO, with lower morbidity, respiratory infections, and diarrhoea.[30-34] 2'-FL-positive breast milk has also been shown to help alleviate the effects of caesarean birth on infant gut microbiota in a study that investigated the differences between gut-microbiota composition in infants with mothers that secrete milk with high 2'-FL content (secretors) and those with mothers who do not (nonsecretors), taking into account birth mode. It found that many of the caesarean-associated dysbiosis patterns were more pronounced among the infants of nonsecretors compared to those of secretors; particularly, bifidobacteria were strongly depleted and enterococci increased amongst this group.[35] In the same cohort, these findings relate to the observed reduced risk to manifest IgE-mediated allergic symptoms in caesarean-born infants breastfed by mothers expressing 2'-FL compared to the nonsecretor-fed infants at 2 years of age.[36]

Benefits of Formula Supplemented with Human Milk Oligosaccharides

Results from a randomised controlled trial showed that feeding healthy infants a formula containing 2'-FL modified their innate and adaptive immune profiles to be similar to that of a breastfed reference group. Similar to the breastfed infants, the infants fed the formula containing 2'-FL had lower inflammatory cytokines compared to those fed a control formula.[37]



Antibiotic use:
NNT 6 (95% CI: 3–23)

Bronchitis:
NNT 6 (95% CI: 4–0.75)

Figure 2: Number of infants with >1 event during first year of life.
Lower morbidity, particularly bronchitis, and antibiotic use were reported in infants fed formula supplemented with 2'-fucosyllactose and lacto-N-neotetraose versus control formula.

NNT: number needed to treat.

Adapted from Puccio et al.[38]

A study by Puccio et al.[38] explored the effects of infant formula supplemented with 2'-FL and LNnT on growth and morbidity in healthy infants. In this multicentre trial, healthy, full-term infants who were not breastfed and aged 0–14 days at the time of enrolment were randomised to receive regular infant formula supplemented with 2'-FL and LNnT (n=88) or a control formula (the same formula without the HMO; n=87). The study met its primary endpoint, showing the formula with 2'-FL and LNnT was well tolerated and supported normal growth in healthy infants for a 4-month period. Secondary findings showed that infants fed the two HMO formula had significantly lower rates of parent-reported morbidities related to LRTI, particularly bronchitis, as well as reduced antibiotic and antipyretic use for a 12-month period compared to those fed control formula (Figure 2).[38]

In the same study, Berger et al.[39] then investigated whether HMO-driven microbiota changes relate to the observed reduced risk for reported antibiotic use and LRTI. They compared microbiota composition at 3 months of age across the two randomised formula-fed groups (regular formula supplemented with 2'-FL and LNnT and control formula) and a breastfed reference group. Results showed that the microbiota composition in infants fed HMO-supplemented formula was closer to that of the breastfed reference group than those fed control formula, mainly because of increases in *Bifidobacterium* concomitant with decreases in *Escherichia* and *Peptostreptococcaceae*.[39]

Furthermore, looking at the association of the microbiota community type with reported morbidities and medication use up to 12 months, formula-fed infants with a community type resembling that of breastfed infants at 3 months were significantly less likely to need antibiotics during the first year than those with the distinct community type typical of control formula-fed infants. This suggests that the reported lower rates of infection-related medication use with HMO may be linked to gut microbiota community types.[39] Although the researchers did not observe any significant association between other reported clinical parameters and the 3-month community type, the caesarean-delivered infants showed more differences between formula

groups than the vaginally delivered infants, suggesting a stronger normalisation effect of the two HMO on dysbiotic microbiota.[39]

Further exploration of possible gut microbial mechanisms that relate to the beneficial clinical outcomes in infants fed formula enriched with 2'-FL and LNnT also showed higher levels of acetate per total SCFA and specific *Bifidobacterium* species at 3 months in the stools of infants who did not experience bronchitis or any LRTI during the first year.[40] In summary, Dr Sprenger noted that findings in formula-fed infants suggest the HMO 2'-FL and LNnT help protect from LRTI and antibiotic use, likely in part through their effects on the early-life gut microbiome establishment and function.

New Data on the Benefits of Human Milk Oligosaccharides in the Management of Cow's Milk Protein Allergy

Professor Anna Nowak-Wegrzyn

Breast milk is the gold standard of infant nutrition. It has the capacity to influence immune-related outcomes in infancy and early childhood and contains many immunomodulatory ingredients including HMO, which provide the substrate for the developing gut microbiome of infants. More than 200 HMO have been detected to date, and a large Finnish study has suggested that the profile of HMO in breast milk may influence development or may be a risk factor for development of CMPA. This study found that the breast milk of mothers whose infant had CMPA had a different composition of HMO compared to mothers of nonallergic infants.[41]

The two HMO, 2'-FL and LNnT, have been selected for inclusion in the new generation of infant and specialty formulas to more closely emulate the profile of breast milk. Prof Nowak-Wegrzyn reviewed new evidence supporting the addition of HMO as an important component of a hypoallergenic whey-based extensively hydrolysed formula (EHF) for the management of CMPA. The IVORY trial was the first clinical trial of a whey-based EHF containing two HMO in CMPA, designed to evaluate its hypoallergenicity. This multicentre, randomised clinical trial included 67 infants and children aged between 2 months and 4 years with physician-diagnosed IgE-mediated CMPA and who were healthy and born at term. It compared currently marketed EHF without HMO with the newly modified EHF supplemented with 2'-FL and LNnT; this was slightly different in that it had a lower content of whey protein: 2.2 g/per 100 kcal versus 2.5 g/100 kcal in the current EHF. Results showed the new HMO-supplemented EHF met the American Academy of Pediatrics (AAP) criteria for hypoallergenicity, being tolerated by >90% of subjects.[42]

Benefits of Human Milk Oligosaccharides Extend to Infants with Cow's Milk Protein Allergy

Research suggests that HMO protect against infection, both in breastfed and healthy infants fed formula supplemented with two HMO. Infants exclusively breastfed for at least 4–6 months had a lower incidence of upper respiratory tract infection (URTI), LRTI, and gastrointestinal infections compared to fully formula-fed infants.[43] This is thought to be related to the immune-modulating and microbiome-modifying effects of HMO.[44] Healthy infants fed a regular formula supplemented with 2'-FL and LNnT since birth had significantly fewer LTRI and required significantly fewer courses of antibiotics in the first year of life compared to those fed a non-HMO containing formula.[38]

Therefore, the next step was to evaluate whether similar benefits would be seen with a hypoallergenic whey-based EHF supplemented with 2'-FL and LNnT in infants with CMPA. Prof Nowak-Wegrzyn described how infants with CMPA and food allergies in general are more susceptible to infections because of the immaturity of their immune system.

The CINNAMON trial[45] was designed to assess whether the newly modified EHF supplemented with 2'-FL and LNnT supports normal growth (primary endpoint) and whether it has beneficial effects on infection rates and related drug use in infants with CMPA.

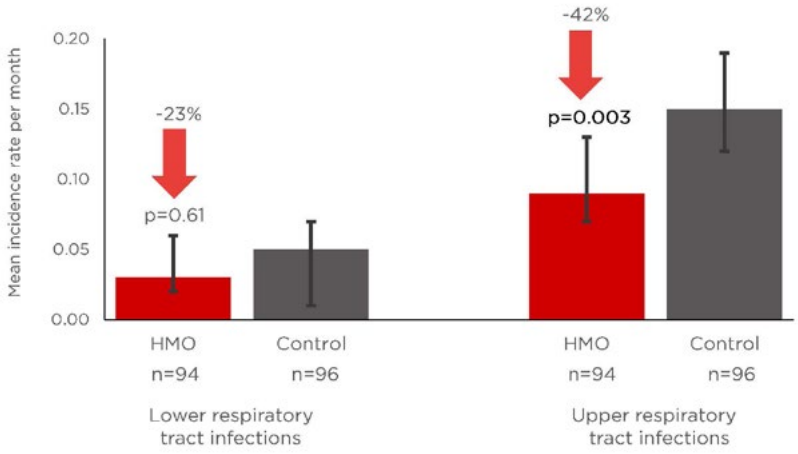


Figure 3: Incidence rate of respiratory tract infections per month of exposure to the whey-based extensively hydrolysed formula supplemented with 2'-fucosyllactose and lacto-N-neotetraose versus extensively hydrolysed formula without HMO (control). Full analysis set (from enrolment to 12 months).[46]

Error bars indicate 95% confidence interval.

HMO: human milk oligosaccharides.

This double-blind, randomised, multicentre, interventional study compared the same two formulas used in the IVORY study and included older infants (aged 0–6 months at enrolment) compared to the Puccio study[38] of the regular formula supplemented with 2'-FL and LNnT in healthy infants. The study met its primary endpoint, with the two groups showing comparable weight gain per day at 4 months (19.38 g/day on test versus 20.12 g/day on control formula).[45]

Prof Nowak-Wegrzyn discussed the secondary outcomes, specifically infection rate, noting that the study replicated many of the observations from the Puccio study[38] in healthy infants. The full analysis set (N=190) showed that the fraction of infants with at least one LRTI from enrolment to 12 months of age was reduced by 33.6% (odds ratio [OR]: 0.61; p=0.25), and URTI episodes were reduced by 5.2% (OR: 0.91; p=0.77) for HMO-supplemented EHF versus control EHF.[46] While the calculated OR were generally in favour of the HMO-supplemented EHF, the confidence intervals were such that those differences were not statistically significant. According to Prof Nowak-Wegrzyn, this may, in part, be because the study may not have been powered to detect these secondary outcomes. Another confounder was the older age at the introduction of the HMO-supplemented EHF in infants with CMPA: the average age was 3.2 months (standard deviation: 1.7) compared with healthy infants fed with the HMO-supplemented formula since birth. The earlier introduction of the HMO-supplemented formula might have a more favourable impact on establishment of a healthy gut microbiota and modulation of infection risk. Risk of otitis media was also reduced by 70–100%, with a significant difference between the HMO-supplemented and control EHF on per protocol analysis (n=147; OR: 0.00–0.44; p<0.05).[46]

Specifically, there was a significant reduction of 42% (p=0.003) in the frequency of URTI episodes to 12 months of age in infants fed the HMO-supplemented EHF compared to those fed control EHF (Figure 3); the frequency of LRTI was reduced by 23% (p=0.61).[46]

Summarising, Prof Nowak-Wegrzyn said it was interesting that these reductions in frequency of infections in CMPA were consistent with reduced respiratory infections amongst nonallergic, healthy infants fed regular formula supplemented with 2'-FL and LNnT since birth. She further stated that these findings support and advance the concept of modifying infant formula to enrich it with the immunomodulatory components that are present in breast milk.

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Abstract Reviews

Herein, we present a collection of abstract reviews from this year's EAACI Digital Congress.

Analysis of Inflammatory Parameters During Asthma Exacerbations and Stable Asthma in Patients With Moderate-Severe Asthma

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Disclosure: Dr Braunstahl has received grants from GlaxoSmithKline, AstraZeneca, Chiesi, Teva; and has received personal fees from GlaxoSmithKline, Sanofi, Novartis, all outside the submitted work. Dr Tramper-Stranders has received IIS grants and personal fees from OM Pharma, outside the submitted work. All other authors have declared no conflicts of interest.

Acknowledgements: The authors would like to thank the enrolled patients for participating in this study.

Keywords: Asthma, exacerbations, immunology.

Citation: EMJ Allergy Immunol. 2020;5[1]:37-39. Abstract Review No. AR1.

BACKGROUND AND AIMS

Asthma exacerbations (AE) are defined as acute or subacute worsening of symptoms from the patient's usual status and are responsible for most of the morbidity in patients with asthma.[1] Allergens and especially viral-associated respiratory tract infections (RTI) are common triggers for AE. Viral RTI account for approximately 40–60% of all AE.[2] Animal studies suggest that during viral-associated AE, an increase of so-called alarmins in the circulation can be found, namely IL-33, thymic stromal lymphopoietin, and IL-25. In humans, an increase of serum cytokines, such as IL-10 and IL-18, and a decrease of serum periostin has been described during AE.[3,4] Immunological mechanisms underlying AE have not yet been completely unravelled.

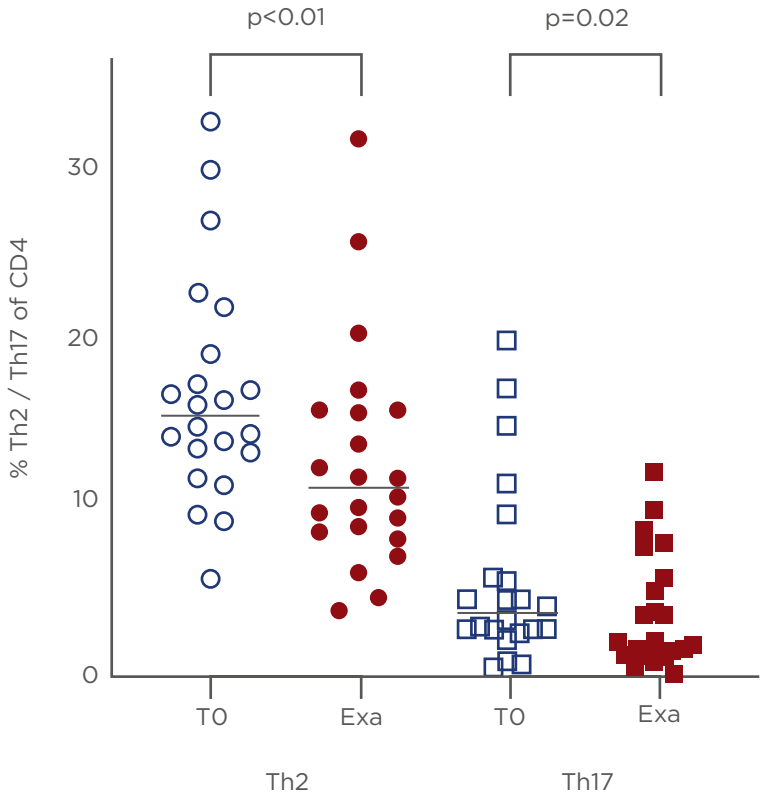

Figure 1: Percentage Th2 and Th17 of T-cells.
Exa: exacerbation; T0: stable timepoint.

In this study, the authors aimed to gain insight into the immunological dynamics of moderate-to-severe exacerbations.

METHODS

Patients from the Breathe study, a double-blind, randomised-controlled trial to determine the effects of a bacterial lysate in patients with Global Initiative for Asthma (GINA) 4 asthma and recurrent AE, were enrolled in the study. Patients were randomised to either 2-year winter season bacterial lysate or placebo treatment. Study visits took place every 3 months, and an extra study visit was planned promptly at the start of an AE. Every 6 months and at the start of during-exacerbation visits, blood was drawn. T2 phenotype was based on T2 inflammation, determined by GINA 2020.[5] Nasopharyngeal swab Amies medium was analysed with multiplex viral PCR, blood leukocyte differentiation was calculated with DxH, plasma cytokines were measured with ELISA, and flow cytometry was used to analyse blood T-cell subsets and intracellular cytokines. Baseline and exacerbation data were compared. Data are shown in median (interquartile range).

RESULTS

Thirty-six patients were included in this study. Asthma Control Questionnaire (ACQ) score increased during an AE. In 43.0% of the exacerbations a nasopharyngeal virus was detected, and pathogenic bacteria were detected in 16.8% of the exacerbations. Blood neutrophils did not alter between AE and baseline, while numbers of eosinophils tended to decrease (4.31 [1.39–6.32] versus 1.35 [0.42–2.88] x10^3/mL; p=0.09). Plasma cytokine analysis showed an increase of IL-10 during an AE (1.95 [1.95–8.85] versus 5.61 (1.95–14.33) pg/mL; p=0.01). Preliminary T-cell subset analysis (n=22) showed a decrease in Th2 and Th17 cell numbers (Figure 1). Intracellular $CD4^+$ T-cell cytokine analysis revealed an increase of percentages

of IL-5 (0.83 [0.60–1.32] versus 1.91 [1.51–4.50]; p<0.01) and IL-9 (0.89 [0.50–2.65] versus 2.44 [0.91–3.01]; p<0.01) and a decrease of percentages of IFNγ (9.85 [6.75–14.93] versus 5.18 [3.62–9.28]; p<0.01). These intracellular effects were most profound in virus-associated exacerbations.

CONCLUSION

In this study, >40% of AE were virus-associated. An increase of IL-5 and IL-9 and a decrease of IFNγ was seen, which is in line with previous literature.[3,4] Moreover, the increase of IL-5 and IL-9 and the decrease of the number of eosinophils combined with a decrease of blood Th2 and Th17 cells during an AE might hint to migration from systemic inflammation to more local inflammation.

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Skin Mycobiome Sequencing Reveals a High Fungal Diversity in Patients With Severe Atopic Dermatitis

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Disclosure: The authors have declared no conflicts of interest.

Keywords: Atopic dermatitis (AD), *Malassezia*, skin mycobiome.

Citation: EMJ Allergy Immunol. 2020;5[1]:39-40. Abstract Review No. AR2.

BACKGROUND

Atopic dermatitis (AD) is a multifactorial, chronic, relapsing inflammatory skin disease.[1,2] Characteristics are an impaired skin barrier and an altered skin immune system, which often come along with predominant colonisation by *Staphylococcus aureus*.[3,4] The role of fungi, i.e., the mycobiome, remains poorly investigated although patients with AD are frequently sensitised to *Malassezia* spp., the most abundant fungus on skin.[5] Through this study, the authors aimed to improve the understanding of the skin mycobiome in AD.

METHODS

Skin swabs of 15 patients with AD (nine mild-to-moderate and six severe cases) and 11 healthy controls (HC) were taken from four skin sites (antecubital crease, glabella, vertex, and dorsal neck). To assess temporal shifts in the mycobiome, patients with AD were sampled at three time points (0, 2, and 4 weeks). HC were sampled at four time points (0, 4, 8, 12 weeks). The authors analysed relative abundance of fungal classes and species by amplicon-based next-generation sequencing of the fungal internal transcribed spacer 1 region. Next-generation sequencing data were analysed with R.[6]

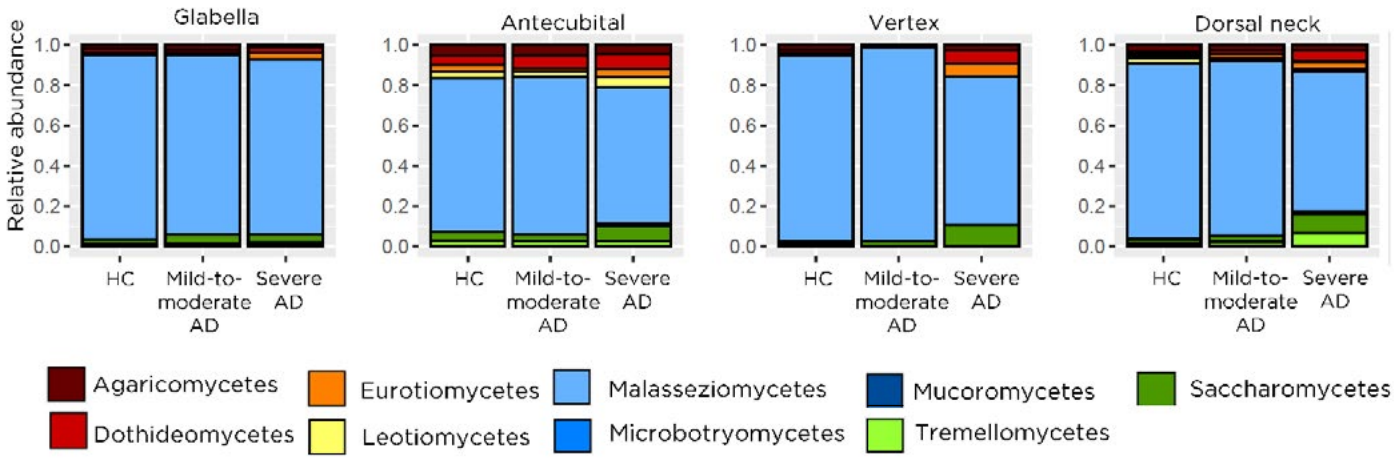

Figure 1: Merged relative abundance of fungal classes of healthy controls, patients with mild-to-moderate atopic dermatitis, and patients with severe atopic dermatitis on four different skin sites: glabella, antecubital, vertex, dorsal neck.

AD: atopic dermatitis HC: healthy controls.

RESULTS

The most abundant fungi at all skin sites were *Malassezia* spp. As shown in Figure 1, patients with severe AD tended to be more frequently colonised with non-*Malassezia* fungi such as saccharomycetes (predominantly *Candida* spp.), whereas patients with mild-to-moderate AD had similar distributions as HC. The *Malassezia* species with the highest prevalence were *M. restricta* and *M. globosa* with a site-dependent distribution. *M. restricta* was most abundant at the glabella and vertex; in contrast, *M. globosa* had the highest abundance antecubital and at the neck. *M. restricta* abundance was decreased in patients with severe AD compared with the other groups, whereas, *M. globosa* was overall equally abundant in the different groups. In most HC and patients with mild-to-moderate AD, the mycobiome was comparable between individuals and stable over time. In contrast, in severe AD the mycobiome was different between individuals and changed over time (data not shown).

CONCLUSION

Patients with severe AD had a high intra- and interpersonal species diversity. The authors speculated that the impaired skin barrier in severe AD allows colonisation with more different fungi than healthy skin. Vice versa, the altered mycobiome may cause activation of the skin immune system leading to inflammation and eczema. In the next step, the authors will correlate these results with the bacterial microbiome in the same samples.

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Does Probiotic Microorganism *Lactobacillus reuteri* Prevent Allergic Rhinitis and Rhinoconjunctivitis Development in Children

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Disclosure: The author has declared no conflicts of interest.

Keywords: Allergic rhinitis (AR), allergic rhinoconjunctivitis (ARC), children, probiotics, primary prevention.

Citation: EMJ Allergy Immunol. 2020;5[1]:41-42. Abstract Review No. AR3.

BACKGROUND AND AIMS

Allergic rhinitis (AR) and allergic rhinoconjunctivitis (ARC) are common chronic disorders in children.[1] They have a strong impact on the quality of life of children.[2] Many studies indicate that colonisation of the gut early in life plays a substantial role in directing immune-system development.[3] Microbial exposure during the perinatal period is linked to the epigenetic regulation of genes involved in allergic inflammation, and it alters susceptibility to allergic diseases. Immune responses in the gut may modulate immune responses in distant target organs, including the nose.[4] Unlike in other allergic diseases, the therapeutic effect of probiotics in AR has been primarily demonstrated, whereas their preventive effects have not been conclusively defined.[5] The objective of this study was to evaluate the efficacy of the probiotic microorganism *Lactobacillus reuteri*-DSM 17938 (LR) in the prevention of the development of AR and ARC in Slovenian children aged 9 years old.

MATERIALS AND METHODS

This prospective, epidemiological study included 316 maturely born infants with a positive history of parental allergy. The children were born between January 2008 and June 2010, were without congenital anomalies, and had a birth weight of at least 3 kg. They were exclusively breastfed for at least 4–6 months. After the fourth month, the same dietary intake for the child and avoidance of probiotics usage was recommended to parents. According to the addition of LR into the child's diet, children were divided into two groups: Group A, 201 children exclusively breastfed, and Group B, 115 children breastfed with addition of LR. From the age of 4 weeks, the mothers of Group B infants added LR to breastfeeding for 12 weeks. Daily, 100 million live LR were given directly into the child's mouth (87.8%) or were applied on the mother's nipple while breastfeeding (12.2%). Every child was followed up by the same paediatrician until they were 9 years old. The prevalence of doctor-diagnosed AR and ARC was observed. The diagnosis was based on clinical history, examination, and allergy testing (elevated specific IgE and positive skin prick tests) performed by a physician unaware of the child's group allocation. Data about frequency and duration of AR and ARC exacerbations were recorded. Chi-squared test with Yates' correction and paired t-test were used for statistical analysis. p-values less than 0.05 were considered significant.

RESULTS

At 9 years, the prevalence of AR and ARC in the study group was 19.6% (10.4% of children had AR, 9.2% had ARC). The difference in the prevalence of two diseases was nonsignificant ($p>0.05$). No significant sex-specific difference in AR (males: 11.0%; females: 9.8%) or ARC (males: 6.7%; females: 11.7%) prevalence was found ($p>0.05$). The prevalence of AR was significantly lower in Group B (13.9% [A] versus 4.3% [B]; $p=0.01$). No significance between group difference in ARC prevalence was confirmed (9.5% [A] versus 8.7% [B]; $p>0.05$) (Figure 1). Lower frequency (episodes/child: 6.3 [A] versus 4.6 [B]) and shorter mean duration (days/episode: 13.9 [A] versus 11.4 [B]) of AR exacerbation episodes in Group B were observed ($p<0.01$).

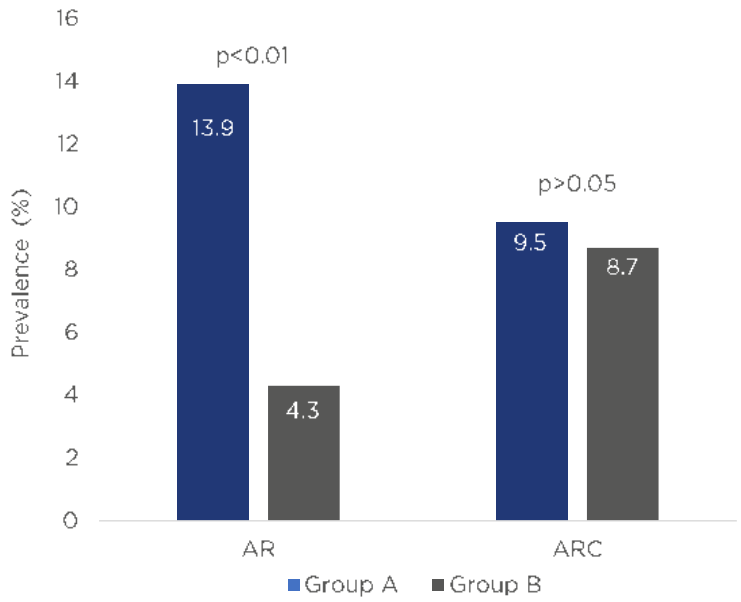

Figure 1: Prevalence of allergic rhinitis and allergic rhinoconjunctivitis in each group of infants.

AR: allergic rhinitis; ARC: allergic rhinoconjunctivitis.

The between group difference in frequency (5.9 [A] versus 6.0 [B]) and duration (15.8 [A] versus 16.5 [B]) of ARC exacerbations was insignificant (p>0.1).

CONCLUSIONS

The study confirms that early-life supplementation with LR is efficient in the primary AR prevention; additionally, it has beneficial impact on the course of AR. However, the study failed to demonstrate a positive effect on occurrence and course of ARC.

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Dynamic and Behaviour of Plane Tree Pollen and Its Relationship with Pla a 1 Aeroallergen Concentration in Évora, Portugal

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Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: This work received the support of the Portuguese Foundation for Science and Technology (FCT) through the ICT (Institute of Earth Sciences) project UIDB/04683/2020, the Pollensorb Project (PTDC/ATPEAM/0817/2014), the Spanish Ministry of Science, Innovation, and Universities through the project SICAAP-CPI RTI2018-096392-B-C22, the UCLM through the UCLM Plan Propio, the Castilla-La Mancha Regional Government, the European Social Fund (ESF), and the Youth Employment Initiative (YEI) for the postdoctoral grant for Dr Lara.

Keywords: Airborne allergen, human respiratory allergy, Pla a 1, *Platanus* pollen, pollen allergy in urban environments.

Citation: EMJ Allergy Immunol. 2020;5[1]:43-44. Abstract Review No. AR4.

BACKGROUND AND AIMS

Platanus pollen is an important cause of allergy in many cities of western Europe, where this pollen is produced by the plane tree, *Platanus orientalis* L. var. *acerifolia* Dyand (Aiton), which is widely used as an ornamental species in parks, gardens, and other urban green areas,[1] favouring human exposure to its pollen. Its major allergen Pla a 1 is recognised by up to 92% of monosensitised *Platanus* allergic patients and 83% of polysensitised patients, allergic to this pollen type, present 60% of IgE to its major allergen Pla a 1.[2] In this study, the authors studied this pollen type and the allergen Pla a 1 in the year 2018 in the atmosphere of Évora, Portugal. The aim was to analyse the aerobiological characteristics of the *Platanus* pollen and to study the relationship between the airborne concentration pollen and the major allergen Pla a 1. Furthermore, the influence of meteorological variables on the airborne concentration of this pollen type was investigated.

MATERIALS AND METHODS

Pollen and allergen sampling were performed using a Hirst-type spore trap (Lanzoni S.r.l., Bologna, Italy) and a high-volume cascade impactor ChemVol® (Butraco, Son, the Netherlands), respectively. Pollen was analysed following the procedure established by the European Aerobiology Society (EAS) and following the approach recommended in Galan et al.[3] Allergens were quantified using a specific ELISA method.[4] The main pollen season was calculated as 95.0% of total annual pollen, obtained after removing 2.5% of the start and end of total annual pollen integral.[5] Meteorological data were obtained from the Atmospheric Sciences Observatory (ICT), University Évora, Évora, Portugal.

RESULTS

The results indicate that the main pollen season of the *Platanus* pollen took place from March 28th to April 20th. The maximum concentration was recorded on April 1st with 619 pollen grains/m^3. There were 16 days of allergy risk (>50 pollen grains/m^3) for people with allergies, of which seven were considered as high-risk level (>200 pollen grains/m^3).[6] Regarding Pla a 1, the temporal profile coincided and a significant relationship between the concentration of airborne pollen and allergen was found (Spearman's R=0.632; p<0.01). The mean pollen potency[7] was 14.4±7.7 pg allergen/pollen.

Table 1: Spearman´s correlation analysis between pollen and meteorological variables considering different time lags.

Lag-time	Temperature maximum (ºC)	Temperature minimum (ºC)	Precipitation (mm)	Relative humidity (%)
t	0.123	0.083	0.027	0.110
t-1	0.211	0.082	0.009	0.184
t-2	0.209	-0.005	0.004	0.142
t-3	0.193	0.173	0.198	0.255
t-4	0.378*	0.333	-0.019	-0.026
t-5	0.485*	0.290	-0.188	-0.133
t-6	0.480*	0.295	-0.174	-0.285
t-7	0.413*	0.008	-0.430*	-0.577*
t-8	0.095	-0.009	-0.208	-0.353*

Lag-time is the number of days before the current day (t).
*p<0.05

The temperature, precipitation, and relative humidity (RH) were the meteorological variables that most influenced the airborne *Platanus* pollen in Évora; maximum temperature occurring 4–7 days prior to pollen release positively influenced pollen loads, while precipitation and RH, particularly 7–8 days prior to pollen release, had a negative influence (Table 1).

CONCLUSION

In summary, these results show that the allergenic load (Pla a 1) coincides with the presence and magnitude of the pollen concentration in the atmosphere. Only the meteorological conditions during 4–8 days prior to pollen release were significant, suggesting that the environmental conditions during the pollen maturation process in the anthers are key factors involved in the *Platanus* pollen and allergen emissions and, thus human exposure to its allergens. Finally, the results suggest that pollen counts are good indicators of the allergenic loads in the atmosphere and, together with meteorological conditions, are useful to design allergen forecasts and alert systems for the allergic population.

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Personalised Immunoinflammatory Phenotypes of Children With Viral Bronchiolitis

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Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: The authors would like to thank the study participants and their parents.

Keywords: Acute viral bronchiolitis (AVB), fever, nasal scrapings, peripheral blood mononuclear cell (PBMC), personalised transcriptomics, RNA-seq.

Citation: EMJ Allergy Immunol. 2020;5[1]:45-47. Abstract Review No. AR5.

BACKGROUND AND AIMS

In early life, the immune and respiratory system are functionally immature, presenting a window of susceptibility in which a subset of infants are hypersusceptible to acute viral bronchiolitis (AVB) and at high-risk of frequent hospitalisations,[1,2] for reasons incompletely understood. AVB is characterised by asthma-like symptoms, and clinical presentation is variable and may reflect a heterogeneous syndrome/subphenotypes.[3] Importantly, susceptible infants are more likely to develop chronic pulmonary disease later in life, including persistent asthma.[4] Studies in infants with AVB have been limited and mainly restricted to circulating blood-derived cells in infants aged <24 months.[5-7] Thus, systems-level studies extending to nasal tissues with accompanying personalised immune response profiling are urgently required to advance the understanding of the precise underlying mechanisms of AVB, and to drive development of more precisely targeted therapeutics. The study approach taken in this study[8] (Figure 1) consisted of a comparison of AVB-associated expression profiles in affected infants (aged <18 months) versus older children (>18 months–5 years), encompassing both circulating peripheral blood mononuclear cell (PBMC) and nasal mucosa, the site of primary viral infection. The aim of this study was to characterise the cellular and molecular mechanisms underlying severe respiratory infections in infants and children with AVB.

METHODS

PBMC and nasal mucosal scrapings were obtained from infants (aged <18 months) and children (aged >18 months–5 years) during severe AVB and postconvalescence. Immune response patterns were profiled in a paired design following a battery of analyses (Figure 1): multiplexed plasma cytokines, viral diagnostics, flow cytometry, and transcriptomics (RNA-sequencing). Immune profiling firstly consisted of group-level systems analyses employing upstream regulator and coexpression network analysis. Secondly, potential heterogeneity among individual subjects was identified with personalised immune response profiling using N-of-1-pathways analysis.[9]

RESULTS

Group-level analyses demonstrated that infant PBMC responses were dominated by monocyte-associated hyperupregulated Type 1 IFN signalling/proinflammatory pathways (drivers: TNF, IL-6, TREM1, IL-1B), while in children a combination of inflammation (drivers: PTGER2, IL-6) plus growth/repair/remodelling pathways (drivers: ERBB2, TGFB1, AREG, HGF) coupled with Th2- and natural-killer-cell signalling pathways were upregulated. Potential confounders of molecular signatures, such as steroid usage and variations in underlying viral pathogens, were excluded as contributors to age-related differences between infants and children.

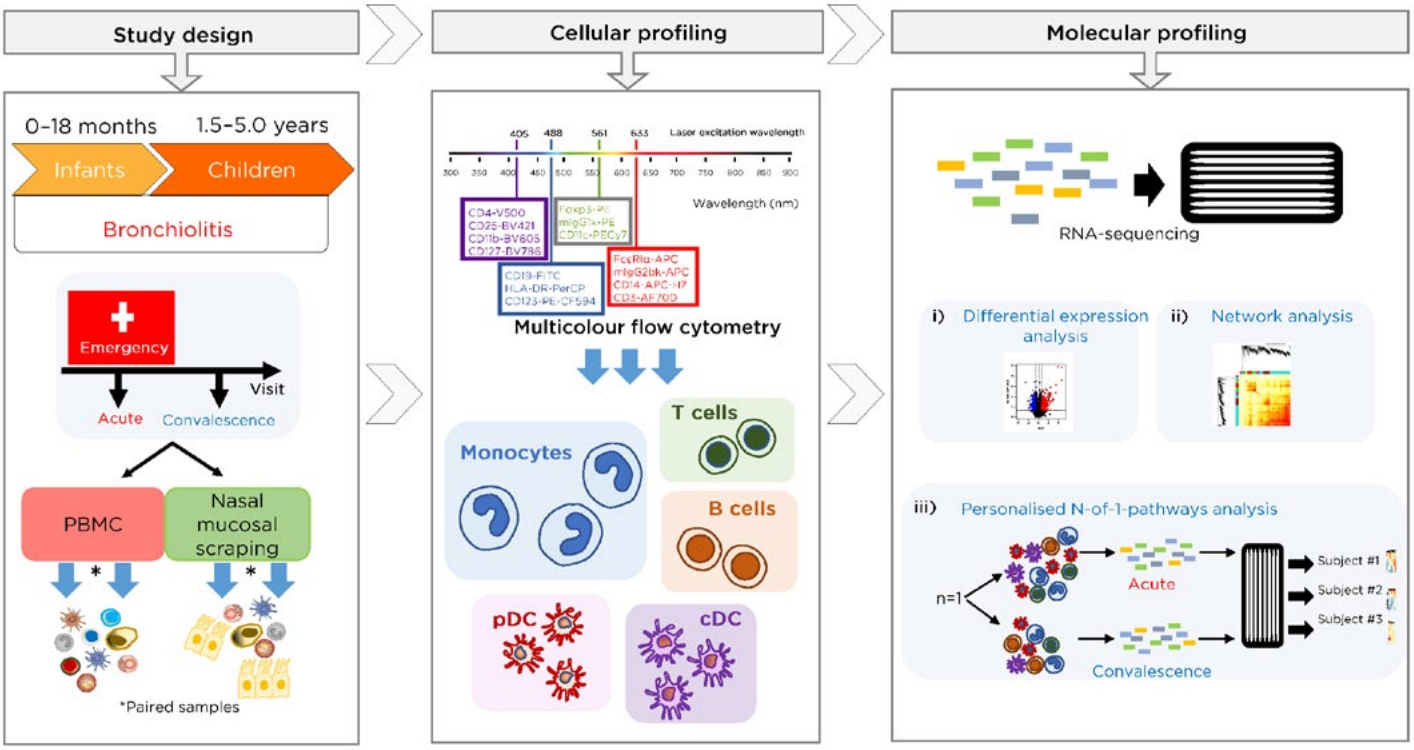

Figure 1: Study design and sample collection at the acute and convalescent visit of infants (aged <18 months) and children (aged >18 months – 5 years) with acute viral bronchiolitis.

Cellular (multicolour flow cytometry) and molecular transcriptomic (RNA-sequencing) profiling was carried out on cells obtained from peripheral blood and nasal scrapings. Analyses included differential expression analysis, network analysis, and novel personalised immune response profiling using N-of-1-pathways analysis.

cDC: conventional dendritic cells; PBMC: peripheral blood mononuclear cell; pDC: plasmacytoid dendritic cells.

In nasal mucosal tissues, Type 1–3 IFN signatures were qualitatively comparable in infants and children; however, the magnitude of upregulation was higher in infants (range: 6–48-fold) than children (range: 5–17-fold). The most intense response profiles were observed in infants manifesting febrile symptoms.[10] Personalised immune response profiling employing N-of-1-pathways analysis confirmed the upregulation of innate immunity in infants and natural-killer-cell networks in children, and additionally unmasked AVB response subphenotypes that were independent of chronological age.

CONCLUSIONS

A defining immunologic characteristic of AVB-susceptible infants was dysregulated expression of IFN-dependent pathways.[8] Moreover, febrile infants showed uniquely complex immunoinflammatory responses during AVB,[10] and a subset of children also demonstrated this IFN-hyperupregulated immunophenotype in peripheral blood. A subcluster of subjects manifesting susceptibility to severe respiratory viral infection in early life are characterised by delayed immune development trajectories, i.e., slow kinetics of postnatal maturation of innate immune competence.

CLINICAL IMPLICATION

Personalised immune response profiling uncovered covert intrasubject variation in immunoinflammatory phenotypes, a pattern which was concealed in 'averaged' expression profiles amongst this age group. Moving forward, personalised transcriptomics may be a key tool to identify risk-associated immunophenotypes and better inform the selection of appropriate targeted treatments.

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Congress Interviews

We spoke to two recent Past Presidents of EAACI about their Presidential terms, their current contributions to the academy, and the progress in their areas of expertise.

Prof Dr. Hab. Ioana Agache

Transylvania University, Brasov, Romania
EAACI Past-President (2017–2019)
EAACI Research & Outreach Committee Secretary

Q1 You are the most recent Past-President of EAACI. What led you to take up such a role, and what were your proudest moments during your term?

I joined EAACI as a junior member some decades ago and I witnessed the academy grow into the most influential scientific organisation in the field of allergy, asthma, and clinical immunology worldwide. I believe that if you have the spirit, empathy, and belief, and you empower peers with similar energy and ideas, together we can accomplish anything that we put our collective minds to. During my presidency, the academy continued to grow in a sustainable way, continuing to build on the traditional EAACI values. However, we have expanded considerably the research and innovation portfolio, the communication and educational tools, and the stakeholder network.

Q2 One of your many contributions to EAACI is being the current Secretary for the Research & Outreach Committee. Please could you tell us about your role and the aims of the committee.

Firstly, the EAACI Research and Outreach Committee (ROC) support allergy, asthma, and clinical immunology research through the coordination and support of the research community. A platform for in-depth knowledge exchange between basic scientists will provide a continuously updated database with the available experimental models with specific benefits, limitations, costs, and availability, and will facilitate research recommendations on allergic disease models with alignment between research centres on standard operating procedures and data quality. Secondly, it will support high-quality and reproducible data by leveraging resources into a joint information exchange

network whilst boosting first-class experimental research through multicentre collaborations and strengthening the validity of the experimental medicine results. This approach will lead to more efficient use of resources and a more significant reduction in the numbers of animals used, thereby enhancing the ethical standards and translational capacity of experimental research. Finally, the EAACI ROC will deliver new forms of translation of key research findings, to better meet the needs of clinicians and more quickly develop precision approaches to improve and cure allergic disease and asthma.

Q3 You were the Project Co-Chair of the newly published EAACI Guidelines on the use of biologicals for severe asthma. What was the rationale for putting these guidelines together, and what are the key take-home messages?

Severe asthma imposes a significant burden on patients, families, and healthcare systems. Management is difficult because of disease heterogeneity, comorbidities, complexity in care pathways, and differences between national or regional healthcare systems. Better understanding of the mechanisms has enabled a stratified approach to the management of severe asthma, supporting the use of targeted treatments with biologicals. However, there are still many issues that require further clarification. These include selection of a certain biological (because they all target almost the same disease phenotype), the definition of response, strategies to enhance the response rate, the duration of treatment, and its cost-effectiveness. The EAACI Guidelines on the use of biologicals in severe asthma follow the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach in formulating recommendations for each product and each outcome. In addition, a management algorithm for the use of biologicals in the clinic is proposed, together with future approaches and research priorities.

Q4 What is the best approach for clinicians to take to ensure they are keeping up to date with the latest guidelines and that they are incorporating them into their day-to-day practice?

It starts with a switch from drug-oriented to patient-oriented research and with involvement from the very beginning of all stakeholders in the guidelines' development process. Then, the recommendations should be clear, concise, and meaningful for the clinician. Last but not least, flexibility with adaptation according the local environment (e.g., resource-constraint settings, cultural beliefs, local policies) should guide the implementation of the recommendations.

Q5 Earlier this year it was announced that EAACI is launching a research platform. What content will this platform host, and how will it facilitate collaboration?

The knowledge exchange platform will facilitate basic and clinical research career development by expanding the funding opportunities for EAACI fellowships, develop educational and training programmes on cutting-edge research methodologies, facilitate access of EAACI members to research funding opportunities, and inform public policy on research priorities in allergic diseases and asthma via public engagement and outreach activities. Finally, the ROC aims to build an infrastructure that will monitor, analyse, and interpret science and research data to identify trends, barriers and opportunities, as well as strategic imperatives, forecast needs, and directions. In addition, this infrastructure will identify, collect, analyse, and disseminate data related to academic allergy and clinical immunology (funding, pipeline) and provide periodic public policy recommendations on behalf of EAACI.

Q6 As a response to the COVID-19 outbreak, EAACI 2020 will now take place virtually. Do you think this will encourage EAACI to host more virtual events in the future?

Not necessarily. I believe that we should keep a balance between live and virtual events in order to ensure direct networking and communication, whilst outreaching remotely to those who cannot attend in person. Whether through personal mobile devices or sophisticated virtual meeting suites, technology is revolutionising the way meeting content is communicated, both in and out of the meeting room. Not only are people outside the room drawn in, but those within the room have access to a heightened degree of interaction. Hybrid meetings are already a

"I believe that if you have the spirit, empathy, and belief, and you empower peers with similar energy and ideas, together we can accomplish anything that we put our collective minds to."

tradition and we will continue on that path.

Q7

COVID-19 is not only impacting clinicians, but also scientific researchers. What impacts will the COVID-19 pandemic have on the course and direction of your research, or the field of asthma in general?

I saw recently a very interesting headline: "The confrontation between the pandemics and the chronic disease." Both healthcare professionals and patients with asthma were caught in the middle and we all had to adapt fast to ensure optimal care for asthma whilst coping with the pandemic's harsh restrictions, meant to ensure safety at a population level. So, we switched as many patients as possible to telemedicine and ensured direct consultations for all those in need, including diagnosis of new cases. The overall goal was to ensure optimal asthma control and accessibility to proper care, either in person or virtually. As for research, it never stopped, because patients with asthma are in urgent need of new medications, although we had to adjust here as well and postpone all unnecessary evaluations until the restrictions are lifted. The major lesson learned is that we have to invest more in the near future in strengthening both the European Union and the national competence in health. Hopefully, more funding will be allocated for medical research, innovation, and quality care for chronic diseases.

Q8

One of your research focusses is asthma phenotypes and endotypes. In your opinion, what have been the most influential developments in this field over the recent years?

The management of severe asthma evolved from the bulk approach to stratified management based on disease phenotypes. However, the burden of the disease did not improve as expected. This is particularly due to the fact that phenotypes do not necessarily relate to or give insights into the underlying pathogenetic mechanisms which are described by the disease endotypes. Based on the major immune-inflammatory pathways involved, Type-2 high, Type-2 low, and mixed endotypes are described for severe asthma, with several shared pathogenetic pathways such as genetic and epigenetic, metabolic, neurogenic, and remodelling subtypes. The concept of multidimensional endotyping as an unbiased approach to severe asthma and precision immunology are new tools facilitating the shift from the stratified to the precision medicine approach.

Prof Antonella Muraro

University of Padua and University Hospital of Padua, Padua, Italy
Chair of the EAACI Guidelines Committee
EAACI Past-President (2015–2017)

Q1 Your term as President of EAACI was during 2015–2017. What was the most rewarding aspect of this position?

The possibility to build strong partnerships among immunologists, clinicians, allied health, and patients, who all share the same vision and work together for the same goals. This model of collaboration was implemented both in the scientific activities, such as the guidelines, and in the academy policy decisions, including the patient's representative in the Executive Committee. It represented a cultural change which gave EAACI a credibility at the general-public level and a leadership role worldwide.

Q2 As the Chair of the EAACI Guidelines Committee, please could you tell us about your role, the committee, and the committee's goals.

As Chair, I ensure that the committee fulfils its main aim: to oversee that the generation of EAACI Guidelines is implemented successfully across the membership. I had the privilege of starting the guidelines initiative in EAACI in 2012, with the first guidelines on food allergy and anaphylaxis published in 2014. This initiative shaped a new cultural approach moving from consensus statements, based on experts' opinion, to evidence-based guidelines following the requirements for evidence-based healthcare and healthcare outcomes according to the Institute of Medicine (IOM) and the Guidelines International Network (GIN). In this regard, guidelines can serve also to guide the decisions of policy makers and payers. Transparency is paramount. Everybody can comment on the final draft guideline forwarded to the public via the EAACI website, and the funding body EAACI should not have any influence on the final content.

In order to ensure that all groups and relevant areas are equally represented, the Guidelines Committee includes an epidemiologist, an allied-health representative, a junior member, two patient representatives, and the Ethics chair as an adjunct member. I would like to take this opportunity to thank all the members of the committee for their hard work and dedication.

Specifically, the committee is responsible for four aspects of EAACI Guidelines: 1) assisting EAACI members in developing proposals for new guidelines and updated guidelines for review and approval by the EAACI Executive Committee; 2) overseeing the consistency of the process and its adequate progress; 3) ensuring the appropriate dissemination of EAACI Guidelines; and, most importantly, 4) facilitating the implementation of EAACI Guidelines.

Q3 Collaboration is of massive importance for scientific progression. Who are the Guidelines Committee currently collaborating with, and what are the associated projects?

The Guidelines Committee has a continuous collaboration with the EAACI groups and members to evaluate the gaps in disease management that should prioritise a new guideline or speed-up revision of an old one. In this regard, we are now launching the revision of the prevention of food allergy guidelines which will be available on the EAACI website in mid-May. The revision of the anaphylaxis guidelines is ongoing. Due to the exciting developments in the area, we are going to revise the guidelines for food allergy diagnosis, which will include the role of molecular allergology, as well as the food allergy management guidelines with in-depth evaluation of the immunotherapy for food allergy.

The closest collaboration is with the methodologists in order to obtain the support from them for the evidence-based appraisal and the systematic review of the studies. The mutual exchange of expertise between clinicians and methodologists is further hugely promoted downstream in any new guideline project to achieve the most comprehensive perspective. However, the most accredited methodological approaches, such as GRADE, are complex and the guideline recommendations are not always well appraised by the ultimate users. The new challenge is now to develop a novel concept of user-friendly guidelines that could facilitate getting the feeling of ownership by the readers and their implementation in daily practice.

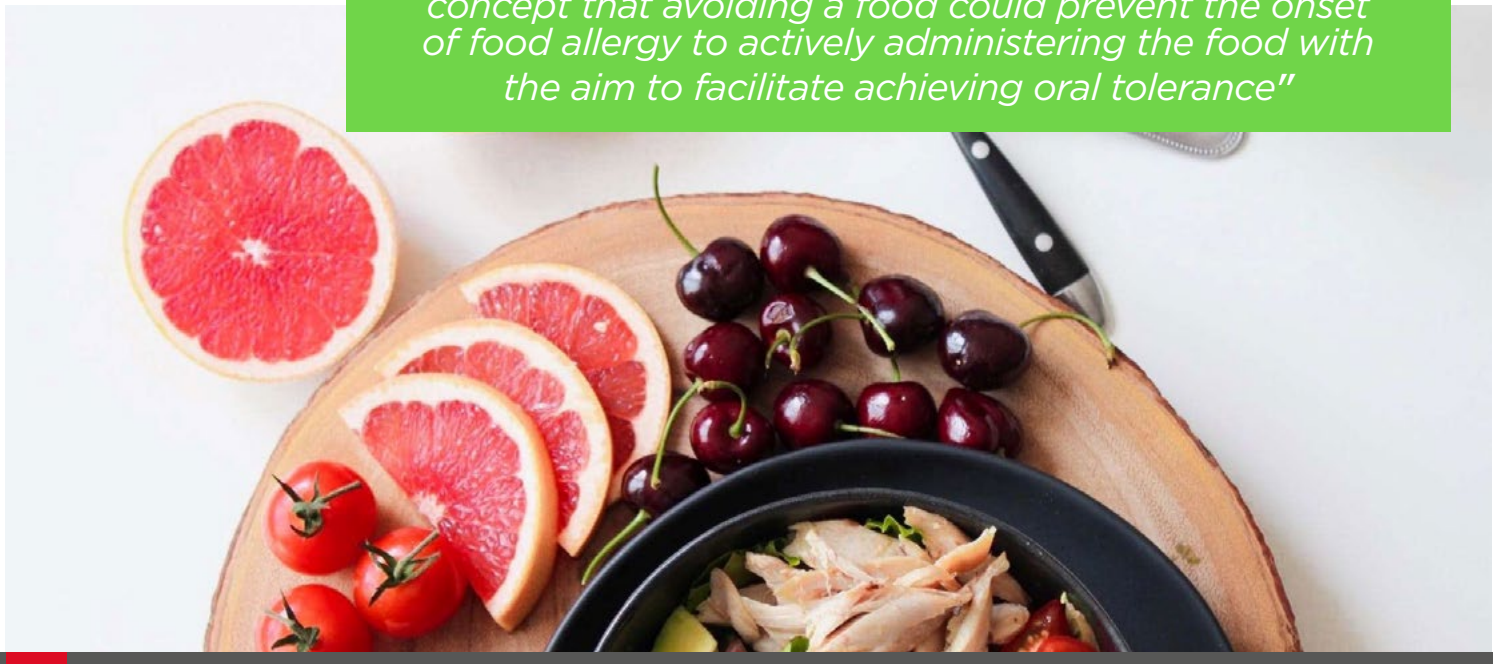
Q1 One of your research interests is the prevention of childhood allergies. In your opinion, what have been the most interesting developments in this field over the recent years?

The crucial change has been the shift from the concept that avoiding a food could prevent the onset of food allergy to actively administering the food with the aim to facilitate achieving oral tolerance. The failure of the avoidance theory, which resulted in an increase of the prevalence of food allergy, has also been recently demonstrated in a pivotal study in the UK LEAP study. Identifying that the skin, especially the eczematous skin, could open the door to food sensitisation and that there is an age-based 'window of opportunity' for introducing complementary food would ultimately lead clinicians to properly modulate the introduction of the right food at the right time. We have revised all the studies in the systematic review on prevention of food allergy, which has recently been published online.[1]

Q5 You were recently involved in the publication of an EAACI position paper about the association between diet diversity and allergy outcomes. What was the rationale for publishing this paper, and what are the main take-home messages?

In the last decade, there has been increasing interest in the role of nutrition on the onset of diseases or maintenance of well-being. Many studies have been conducted on the role of some nutrients, for example fish oil and vitamin D, as well as on the interplay between an early diversification of the diet and the development of allergic manifestations in children and women who are pregnant. Results have been, however, inconclusive, mainly due to the lack of agreed definitions in most of the studies. The aim of this statement is to provide some recommendation by evaluating the association between diet diversity and allergy outcomes (food sensitisation, asthma, allergic rhinitis, atopic dermatitis) in a systematic analysis. According to the knowledge available so far, the paper concluded that diet diversity is recommended for any infant or child, given no evidence of harm and some potential association of benefit in the prevention of allergic symptoms.[2]

"The crucial change has been the shift from the concept that avoiding a food could prevent the onset of food allergy to actively administering the food with the aim to facilitate achieving oral tolerance"



In addition, we hope that the effort to harmonise definitions and set standards for research would serve as basis for collecting good quality data and allow progress in the field.

Q6 Support has been gaining for the potential relationship between the microbiome and allergic diseases. What are your thoughts on this hypothesis?

Our germs are shaping our immune response and many research steps have been performed in elucidating the details involved. During my term as President, EAACI promoted a joint article with the American Academy of Allergy, Asthma and Immunology (AAAAI) on the role of the microbiome in modulating the immune system and influencing onset and severity of clinical manifestations such as asthma, atopic dermatitis, and food allergy.[3] This PRACTALL manuscript intends to provide shared evidence-based recommendations on cutting-edge topics in allergy. Actually, it served also to establish research outcomes for future investigations. I believe that at this stage, however, only networks of big data could provide definite results and possibility of intervention through manipulation of the microbiota.

Q7 The COVID-19 pandemic has impacted numerous clinical therapeutic areas, in particular immunology. Are EAACI putting together guidelines or resources to help educate and advise clinicians with how to either treat COVID-19 or continue treatment of their existing patients?

EAACI has put in place an effort to provide articles with free access at the EAACI COVID-19 resource centre.[4] In addition, the EAACI Section on Pediatrics has recently published a very useful practical guide for managing allergies and immunodeficiencies in children in daily practice.[5]

Q8 In the UK, a law that will require prepackaged foods to be labelled with allergens in more detail will come into effect from October 2021. What impact do allergen labelling laws such as this have on those who have a food allergy?

This will be a landmark step. All patients with food allergies will have the opportunity to check the full list of the ingredients and allergens of prepackaged food. According to the current law, it is mandatory to include in the list of the ingredients only 14 food allergens acknowledged by the European Commission. Patients who are allergic to allergens different from the 14 have still the risk of an inadvertent reaction by accidental ingestion not being able to detect their specific food allergen. This law would reduce the burden for the patients and their families, hopefully preventing anaphylactic reactions and saving lives.

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The Psychosocial Impact of Adolescent Food Allergy: A Review of The Literature

EDITOR'S PICK

Despite improvements in the treatment landscape, the psychological impact of food allergies is still yet to be fully understood. My Editor's Pick for this year's issue is by Newman and Knibb. In this review, the authors discuss the impact of food allergies on the mental well-being of adolescents, including contributing factors to risk-taking behaviour. I hope you enjoy reading this fundamental article.

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Disclosure: Dr Knibb receives consultancy fees from Aimmune. Dr Newman has declared no conflicts of interest.

Acknowledgements: This work was funded by the Midlands Asthma and Allergy Research Association (MAARA).

Received: 07.04.20

Accepted: 28.05.20

Keywords: Adolescence, anaphylaxis, food allergy, peer relationships, psychosocial impact.

Citation: EMJ Allergy Immunol. 2020;5[1]:54-60.

Abstract

Previous research has suggested adolescents and young people with food allergies (FA) have the highest risk of fatal reactions to food. As the prevalence of FA has been increasing there has been increased demand for psychosocial support of adolescents with food allergy, with anxiety around food and social interactions affecting the lives of adolescents and their families. This narrative review aims to explore the psychosocial impact of having a FA in adolescence, including the suggested impact, coping, risk-taking behaviour, and effect of peers and social support. The review concludes with considerations of the wider community which may also have an effect.

BACKGROUND

Food allergy (FA) is defined as an adverse reaction to ingestion of certain food types. The prevalence of FA is currently estimated at 2% of adults and 5–8% of children in the UK.[1] The European Academy of Allergy and Clinical Immunology (EAACI) found that cases of FA have doubled in the last decade.[2] FA-related hospital admissions in the UK have increased 500% since 1990[3] and seven-fold in the last decade.[2] The increase in prevalence may be because of increased identification and awareness. Prevalence rates are also dependent on age and allergen, as it is expected the majority of milk and egg allergies in infants are resolved by school age whereas

nut allergies are likely to persist throughout life,[4] however any food has the potential to become an allergen. An allergy may be IgE-mediated or non-IgE-mediated; IgE are antibodies produced by the immune system that can trigger severe allergic reactions including anaphylaxis, an extreme reaction to an allergenic trigger. Reactions to FA differ by person, however, anaphylactic reactions can be fatal. Adolescents and young adults with a FA are at the highest risk of allergic reactions and mortality,[5-7] and are therefore an essential population to understand and support with their condition.

There is currently no known cure for FA and management includes strict dietary observation and avoidance of possible allergens.[8] If anaphylaxis occurs, an adrenaline auto-injector (AAI) should be used to control symptoms and prevent fatality[9] and an ambulance should be called immediately. It is estimated that 20 people in the UK die each year from a fatal FA reaction.[10]

Anaphylaxis in adolescents caused by FA has received substantial media attention in the UK over the last few years, increasing awareness in its wake. In 2018, 13-year-old Karanbir Cheema had a fatal allergic reaction caused by a classmate placing cheese down their shirt whilst at school.[11] In 2016, 15-year-old Natasha Ednan-Laperouse had a fatal allergic reaction to a take-away baguette that had an incorrectly labelled ingredient list.[12] Following this, there have been campaigns to change food labelling laws.[13] These adolescent fatalities show the severity of FA and the need for policy change in food establishments and schools, as well as a need to educate the public on FA to decrease the risk of fatal anaphylaxis. This narrative review therefore focusses on the breadth of the psychosocial impact of FA on adolescents and explores previous research in this area.

IMPACT OF FOOD ALLERGY IN ADOLESCENCE

DunnGalvin et al.[14] suggests a direct effect on child development. At around 8 years of age, children become aware that parents are unable to ensure complete safety. This occurs in a developmental stage where children are learning to be more autonomous and find their independence as they become adolescent. Between the ages of 8 and 12 years was considered the stage of 'growing awareness'. Through ages 13–16 years, awareness and autonomy grew further as the child adapted to new and unfamiliar contexts.[15] In patients with FA, a conflict in negotiating independence and the power balance between parent and child can cause further anxiety for both.[14] Knowing about these beliefs and challenges associated with having FA in childhood and adolescence may assist in understanding why adolescence is the age patients are most at risk of fatal reactions to food.

Research by DunnGalvin et al.[14] has suggested that FA has an impact on psychological development and theorises that FA affects cognition, emotion, and behaviour, and that these may change and develop as children and adolescents age. Beliefs about identity, or how the participants felt about themselves, shifted at around 8 years of age. Having a food thought of as their 'special' food, as labelled by parents, marked the difference between children and adolescents. The participants felt their FA had a strong impact on who they were as a person and the lives they lived (e.g., friends, places visited, and feelings about the self). Parents, especially mothers, were considered a source of safety for those aged 6–8 years, increasing their confidence in managing the FA. This then shifted after 8 years of age when children started expressing concern over what they ate. Regarding autonomy (independence), control, and self-efficacy (control over themselves and confidence in their actions), children aged ≥9 years realised parents cannot keep them safe in every situation. These feelings of increased risk were exacerbated by the belief that FA severity was not understood by the general population; symptoms were thought to be mild, which made eating out difficult. Food became an area of anxiety as children were concerned that consumption of certain foods would lead to a reaction. This had a higher impact on older participants, especially the fear of being unable to breathe, which was considered the worst symptom. Self-reported FA in the USA between 2007 and 2010 were associated with higher anxiety in adolescents,[16] highlighting a population in need of further support.

Quality of life (QoL) has also been reported to be affected, in both those with FA and their families. A review by Cummings et al.[17] found

strong evidence for the impact of FA on QoL and psychosocial distress in both children and adolescents with FA and their families. FA was found to have an impact on daily life, which included disruption to family activities, concern about eating out, and a preference to continuously visit places perceived as safe, as well as patient and parent concerns about FA management in school.[18] A larger number of allergic conditions (e.g., FA comorbid with eczema) have been associated with a higher report of psychosocial impact, with increasing disruption to social family activities.[19] By contrast, following a negative food challenge, there was a significant improvement in the child and family's social life.[20]

HOW DO ADOLESCENTS WITH FOOD ALLERGY COPE WITH THEIR CONDITION?

As living with a FA can have various psychological and social challenges, adolescents with FA may implement various coping strategies into their allergy management. Sampson et al.[21] found that participants aged 13–21 years considered behavioural strategies such as carriage of their AAI and reading food labels, in addition to communication with others, as the main coping strategies in managing their FA. DunnGalvin et al.[14] identified three coping strategies in FA: avoidance, minimisation, and adaptation. Avoidance strategies focus on reducing stress through avoiding the issue, for example by avoiding places associated with food. This avoidance strategy focusses on the emotions associated with risk and identity. Avoidance strategies were linked with low self-efficacy, meaning adolescents did not feel confident or in control. Avoidance strategies were also associated with high anxiety and a feeling that the FA was a big part of their identity. Cognitive minimisation strategies were more prevalent in boys who experienced bullying. This strategy involved rejection of FA as part of their identity and engagement in 'risky' actions such as not adhering to AAI carriage. By rejecting FA as part of their identity they may also reject the severity of FA, which may lead to more risky behaviour and increased risk of reaction. Finally, adaptive strategies were associated with more positive behavioural, emotional, and cognitive strategies. Adaptive strategies were more common when parents encouraged self-management and independence, which may increase the adolescents' confidence. Positive strategies include supportive peers and good communication, which were felt to be important to adolescents with FA.[14]

ADOLESCENTS WITH FOOD ALLERGY AND RISK-TAKING BEHAVIOUR

Adolescents and young adults with FA have the highest risk of reactions to food and the highest frequency of fatal reactions.[5,7] This may be attributed to increased engagement in risk-taking behaviours,[9] for example not carrying an AAI. Younger children have shown less anxiety and risk-taking behaviour as they depend on parents for FA management. At around 12 years of age, conflict and resentment can arise as adolescents seek independence,[14] which may be why risk-taking behaviour increases.

Sampson et al.[9] suggested that risk-taking behaviour may be a core factor that results in adolescents having the highest risk of fatal anaphylactic reactions. Adolescent risk factors are thought to be influenced biologically by genetic predispositions, direct hormonal influences, asynchronous pubertal timing, and brain and central nervous system development.[22] Risk-taking has also been associated with disinhibition and a risk-taking personality, and, to a lesser degree, experience-seeking, invulnerability, thrill and adventure seeking, and boredom susceptibility.[23]

In psychology, learnt, developmental, and personality approaches have been considered to attempt to explain risk-taking behaviour.[23] The developmental approach considers that risk-taking is either a normal exploratory behaviour or a negative by-product of egocentrism in cognitive development. The learnt approach considers risk-taking an act of deviance in problem behaviour,[24] as a result of a poor environment, family communication, and socialisation.[25] In addition, adolescents who had a personality trait of 'sensation-seekers'[26] were more likely to view risk positively, especially adolescent males.

Previous research on adolescents and risk tends to focus on common coming-of-age risk-taking behaviours such as smoking, alcohol use, and unprotected sex. The more favourable an option was believed to be, the less risk was associated

with it,[27,28] which can be exacerbated by peers with similar views who may reinforce this risk-taking behaviour. While some risk-taking in adolescence is to be expected as young people find their independence, in those with FA, some risk-taking behaviour can have poor health consequences. Warren et al.[29] found adolescent risk-taking behaviour included eating food with 'may contain' labels, not carrying their AAI, kissing people who had recently consumed their allergen, or eating homemade or unpackaged food where they were unsure if it contained their allergen. Findings suggested that adolescents with FA were less likely to engage in risk-taking behaviours if they had a peanut allergy, overprotective mothers, teachers who were aware of their FA, supportive female friends, an established education plan, or a history of being bullied. Positive views of FA, including improved diet, empathy, and greater responsibility, also reduced risk-taking behaviour. A healthier diet may have helped the adolescents feel more positive about their FA diet restrictions, leading to heightened empathy, responsibility, and maturity.

A new potential treatment for FA may also have future effects on risk-taking behaviours. A new oral immunotherapy treatment for children aged between 4 and 7 years has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of peanut allergy.[30] Emergence of desensitisation treatments may affect management of FA and both reduce anxiety and increase QoL in adolescents with FA, which may, as a result, increase risk-taking behaviour. Research exploring psychological and behavioural effects of emerging oral immunotherapy treatment on adolescent FA is essential for understanding future psychosocial impact of FA.

PEERS AND SOCIAL SUPPORT

Peer relationships are an important aspect of adolescent development and can have an influence on adolescent and risk-taking behaviour in both a positive and negative way, depending on peer norms.[30] Peers described as 'deviant', who engaged in delinquent or antisocial behaviour, have been linked to increased risk-taking behaviour in 11–15-year olds.[31]

Support for adults who have FA and have experienced anaphylaxis is viewed as important, though lack of understanding can make this difficult.[32] The literature on peer support for adolescents with FA is lacking, but Warren et al.[33] suggested supportive female friends led to less risk-taking behaviour. Previous research suggests peer pressure may be an issue.[9] This highlights that a good peer support network may have protective factors for adolescents with FA, potentially leading to fewer reactions caused by risk-taking behaviour. In the Sampson et al.[9] study, greater peer education was suggested as a way to reduce teasing and bullying and improve general safety. Bullying focussed on the adolescent's FA, with acts such as throwing the food at the adolescent or threatening them with consumption, as highlighted by Stensgaard et al.[34] Fenton et al.[35] also found that adolescents with FA were sometimes concerned that disclosing they had a FA may affect their safety or jeopardise friendships. However, education may be difficult for adolescents with FA to deliver to their peers themselves. Peer support may help adolescents with FA to reduce risky behaviour and keep safe.

The sensitivity of social relationships with peers and parents for personal development in the adolescent period can have a negative impact on QoL in adolescents with FA.[16,36] Children with FA have been reported to have worse QoL in social and psychological domains, compared to parents.[36] Social limitations in FA have been highlighted in children of various ages, including playing at friend's houses, sleepovers, parties, field trips, and also in family social events.[37] This highlights the importance of building strong relationships with peers and family to reduce social limitations for adolescents with FA.

SCHOOLS

A school environment can also pose a risk for someone with FA. Over 25% of European school children have an allergy and 20% of FA reactions occur in schools.[38] Furthermore, up to two-thirds of schools have a minimum of one child at risk of anaphylaxis, and may not be suitably prepared in the event of a reaction.[38] Food Allergy Research and Education (FARE) report that 15% of American school-aged children with FA have had an allergic reaction in school.[39] Previous

research highlights that schools are the most common location for anaphylaxis.[7,40,41] All schools should have a protective policy in place for their students with FA, however many of these policies could be improved. Personalised emergency management plans that detail individual reaction symptoms and a plan of action for when they occur are not consistently provided[41] and teachers are reported to have poor knowledge about anaphylaxis, including symptoms, triggers, and AAI.[42,43] However, much of this research was carried out in America, and therefore there may be differences when compared to other countries.

In Canada, adolescents reported that the transition to secondary school was difficult as schools were larger and less organised, which made them feel less safe.[44] School policies could also be exclusionary, where adolescents with FA had to sit alone at lunch or were not allowed to attend school trips.[43,45] Finding their FA embarrassing or shameful can create issues in the school environment, especially if peers are unaware of the FA,[9] as adolescents with FA may be secretive to protect themselves or avoid unwanted attention. School trips have also been described as difficult and annoying if the adolescent with FA could not eat "the same as everyone else."[33] When schools were accommodating of FA, children felt safer and more included,[45] however, this also drew attention to how they were different from their peers.[44] Understanding peer beliefs may assist with these issues by suitable school-based interventions.

WIDER COMMUNITY

Adolescents with FA may experience a reaction in a variety of community settings such as restaurants, beaches, sports fields, or gymnasiums,[40] as well as potential fatalities in restaurants, a friend's home, or work.[10] Allergen avoidance training often considers avoidance of allergens in the home, but focusses less on how to avoid exposure to allergens in the community.[46]

Knowledge and attitudes of the community can be a barrier for those with FA, particularly in those who directly interact with consumer food. Confusion has been reported in UK takeaway staff,[47] who were unsure of the difference between milk allergy and lactose intolerance and whether allergens could be transferred by hands. A USA study on restaurant workers showed that very few knew how to assist someone experiencing anaphylaxis and staff were not ready to manage FA safely.[48] These attitudes were similar in European countries such as Germany.[49] Further research into food handlers[50,51] also found knowledge could be improved, and suggested that allergy knowledge was significantly correlated with practice, confidence, and care of workers.

Improved FA knowledge of the general public would be beneficial, is desirable,[46] and must accommodate the general public's needs whilst balancing protection of those with FA. This is an important concern in the UK as well as in other developed countries such as the USA, Canada, Australia, and New Zealand.[52] However, some policies have already been met with resistance, such as nut bans in schools.[53] Nut bans in schools are claimed to be extreme and limiting of food choice by those without FA, as documented in the Canadian study by Harrington et al.[54] In this study, peanut bans faced backlash as peanut butter is an accessible and affordable source of protein in low-income families. In the UK, advice from charities such as Anaphylaxis Campaign[55] is not to use allergen bans, as there is no guarantee it could be a safe environment as children can accidently bring in the banned food from home. This can also create conflict between parents, which may actually increase risk of reaction. As conflict and social exclusion are concerns for those with FA, community interventions should be conducted delicately.[46] As there are different governing bodies for health and education, cooperation between healthcare professionals such as doctors and dietitians, the school community, and parents are necessary to overcome these barriers.[46,56] Community interventions may involve addressing misinformation, providing education, and addressing FA condition beliefs, for example that FA is not a serious condition. Jones et al.[57] found that support groups for young people with FA resulted in improved self-esteem and confidence, both generally and when managing their FA. These groups helped adolescents feel included and share experiences with people who also had FA, which was highly valued. Furthermore, support groups and anaphylaxis management plans were associated with good

adherence to self-care behaviours,[58] leading the authors to suggest these supportive and applied planning elements may be more useful in related interventions rather than interventions focussing on increasing knowledge.

CONCLUSION

FA is a condition of interest and concern because of its rising prevalence, increasing reports of psychological distress, and increasing parental conflict regarding developing independence in adolescence. Adolescence is the age group most at risk of anaphylactic reactions, but it is not yet fully understood why. Understanding the experiences and feelings of adolescents about FA is important to give insight into how adolescents both with and without FA think and feel about the condition. This may also provide suggestions on how to reduce risk-taking behaviour, improve adherence to AAI carriage, and reduce the likelihood of anaphylactic reactions. This may also identify areas where adolescents need more support; for example, in managing their FA as they become more independent and keeping beliefs realistic rather than destructive, such as unrealistic optimism (believing a reaction will never happen to them) or the belief they are surrounded by danger, leading to high levels of anxiety.

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Erythroderma: A Manifestation of Cutaneous and Systemic Diseases

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Disclosure: The authors have declared no conflicts of interest. The institutional ethical board of UMT approved this study.

Received: 17.10.19

Accepted: 12.02.20

Keywords: Emergency, erythroderma, psoriasis.

Citation: EMJ Allergy Immunol. 2020;DOI/10.33590/emjallergyimmunol/19-00182

Abstract

Introduction: Erythroderma, or generalised exfoliative dermatitis, is a rare inflammatory disorder characterised by generalised erythema, involving more than 90% body surface area accompanied by a variable degree of scaling.

Objectives: This retrospective study aimed to determine characteristics of erythroderma as a marker of cutaneous and systemic disease and to identify the underlying causes of this condition.

Materials and methods: Hospitalised patients diagnosed with erythroderma at the dermatology and venereology department of UHC 'Mother Teresa' from 2012–2017 were selected for this study. Epidemiological, clinical, laboratory, and histological data of these patients were electronically compiled and analysed using SPSS© software (IBM, Armonk, New York, USA).

Results: 116 patients were diagnosed with erythroderma. Of these, 43.1% were female and 56.9% were male. The average age of onset was 55.1 years. A variable hospitalisation period was observed from 1–49 days. Previous episodes of erythroderma were indicated in 11.2% of cases, and 29.3% of cases appeared as emergencies. The most common cause of erythroderma was exacerbation of pre-existing dermatoses, namely psoriasis (53.4%), eczema (3.4%), and dermatitis (10.3%). Drug hypersensitivity reactions were evidenced in 4.3% of cases. In 16.4% of cases, the cause of erythroderma was undetermined. This study demonstrated a high percentage of secondary erythroderma to a pre-existing cutaneous pathology, psoriasis in 53.4% of cases, and a low percentage of primary erythroderma.

Conclusions: Erythroderma can be a manifestation of systemic and cutaneous diseases, but mostly erythrodermic psoriasis. Often it presents as a life-threatening emergency. The condition masks the primary pathology lesions, making it difficult to establish the correct diagnosis of the underlying aetiology. However, biopsy provides a positive correlation between clinical findings and anatomopathological diagnosis.

INTRODUCTION

Erythroderma, or generalised exfoliative dermatitis, is a rare inflammatory disorder characterised by generalised erythema, involving more than 90% of the body surface area accompanied by a variable degree of scaling.[1] Erythroderma can be a primary condition, when the cause is unknown, or a secondary condition, caused by known diseases. The age of its onset is related to its underlying aetiology, which in most cases are skin diseases or disorders, hypersensitivity towards drugs and medications, systemic diseases associated with cutaneous erythema, and in rare instances, malignancies. Erythroderma predominates in males and most commonly manifests in older ages. It is a potentially life-threatening disease as it alters cutaneous functions, therefore erythrodermic patients require hospitalisation, rigorous monitoring, and follow-up. Determining the underlying cause of erythroderma is important in choosing the right treatment for these patients.

AIM

This retrospective study aimed to identify the underlying cause of erythroderma and to determine for the first time its epidemiological, clinical, and laboratory features in Albanian patients with erythroderma.

MATERIALS AND METHODS

The authors conducted a retrospective analysis of a total of 116 patients diagnosed with erythroderma at the dermatology and venereology department of UHC "Mother Teresa" from 20122017. Diffuse erythema, (over 70–90% of body surface) accompanied by various degrees of scaling and pruritus, were used as the diagnostic clinical criteria. Epidemiological characteristics, clinical symptoms, performed examinations, skin biopsy, immunophenotyping (whenever indicated), and follow-up information were collected. Emergency and relapse cases were also highlighted when this information was available. The collected data were electronically analysed using SPSS v.19.

RESULTS

Epidemiology

During this 6-year study, 116 patients were diagnosed with erythroderma and admitted to the authors' department. The age of the patients varied from 2–86 years, with a mean onset age of 55.1 years and the highest incidence of erythroderma occurring in the 61–70 age group (26.7%; n=31). There was a slight male predominance with a male to female ratio of 1.32:1.00 (57.0% male versus 43.0% female). There was no change regarding the age of onset of erythroderma in males and females using the independent t-test. Both groups exhibited a highest frequency of erythroderma onset in the seventh life decade. Considering all cases, the total number of patients hospitalised during the period of July and August was higher compared to other months (16.4% versus 14.7%, respectively).

Clinical Parameters

Patients were hospitalised in the department of dermatology for an average of 12.6 days (day range: 1–49 days) following onset of erythroderma. A shorter hospitalisation period was observed in patients with drug-induced erythroderma and a longer hospitalisation period in erythrodermic psoriasis patients. A history of previous erythrodermic episodes was noted in 11.2% of cases (n=13), 10 of which were caused by psoriasis, with the other three being caused by other pathologies, namely chronic eczema, subcorneal pustulosis, and chronic dermatitis. The majority of admissions were planned admissions, however 29.3% of all the cases presented as emergencies.

Clinical Findings in Admission

In the first clinical examination, generalised erythema, scaling, and pruritus were identified. Scaling and erythema are constant identifying markers of the pathology and will be found in 100.0% of cases. Pruritus was detected in all patients, and 34.5% of cases (n=40) had fever >38.5 °C during the onset of the erythrodermic episode. Changes in the nails, psoriatic arthritis, and palmoplantar keratoderma were findings that prevailed in patients with erythrodermic psoriasis in almost 27.6% of cases (n=32) (Figure 1).

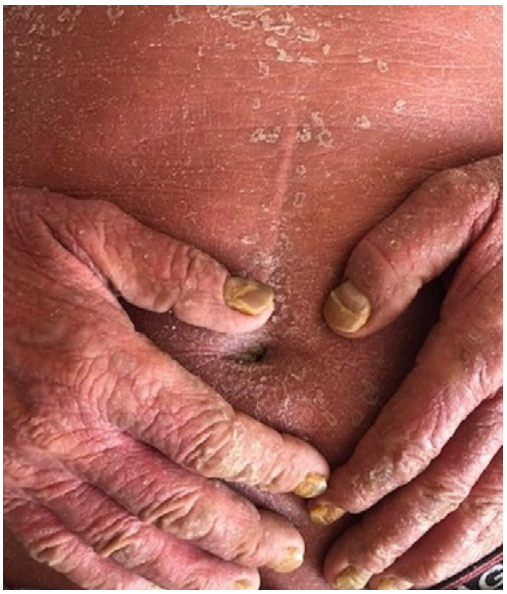

Figure 1: One of the patients with erythroderma caused by psoriasis vulgaris.
(This photo was taken and used in thestudy with the patient's permission).

Laboratory Findings

The most common abnormalities found in the patients included increased erythrocyte sedimentation rate and C-reactive protein in 93.1% of cases (n=108), leukocytosis in 43.9% of cases (n=51), and decreased haemoglobin in 30.2% of cases (n=35).

Cutaneous biopsy was performed in 105 patients (90.5%). In the remaining 11 cases, when the cause of erythroderma was clear at the time of the examination, biopsy was unnecessary. This group included six cases previously diagnosed with psoriasis and five cases of generalised erythroderma appearing after the use of a new drug.

Histopathological examination was decisive for concluding the diagnosis in 86/105patients who received biopsy. The results were as follows: psoriasis vulgaris (53.4%) in 62 cases, psoriasiform dermatitis (6.9%) in eight cases, subcorneal pustulosis (5.2%) in six cases, drug hypersensitivity (4.3%) in five cases, chronic eczema (3.4%) in four cases, chronic dermatitis (2.6%) and erythema multiforme (2.6%) in three cases each, pityriasis rosea (1.7%) and pytiriasis rubra pilaris (1.7%) in two cases each, and spongiotic dermatitis (0.9%) and ichthyosis (0.9%) in one case each. Nonspecific histopathological features were observed in 19 cases (16.4%).

Final diagnosis was based on evaluation of the clinical, biochemical, and histological findings, as well as the development of erythroderma in each individual patient. The most common underlying cause was exacerbation of pre-existing dermatoses, including psoriasis in 59.0% of the cases, subcorneal pustulosis in 5.2%, pityriasis rubra pilaris 1.7%, chronic dermatitis in 3.4%, and pityriasis rosea in 1.7%. Drug hypersensitivity was seen in 4.3% of cases and no cause could be identified in 16.4% of cases. Diagnosis of idiopathic erythroderma was made in patients who manifested an extended condition with the typical clinical signs of generalised erythema, severe pruritus, and scaling. In these cases, the significance of histopathological examination is emphasised. The most important differential diagnosis in idiopathic erythroderma is cutaneous lymphoma, especially in older adult males with an extended and relapsing course of pruritic erythroderma. Close monitoring and repeated biopsy in cases with no found cause of erythroderma may reveal an undiagnosed cutaneous T-cell lymphoma (CTCL). In these cases, histopathology results were nonspecific, and as such were diagnosed as idiopathic erythroderma.

The relationship between a drug and drug-induced erythroderma was decided from a carefully conducted anamnesis with the patient, monitoring the intake of a suspected drug in the days prior to the onset of erythroderma and clearing of the cutaneous manifestations following discontinuation of the specific drug.

On follow-up, no cases of death were recorded due to erythroderma or its underlying causes. Relapse was observed in patients with chronic dermatitis and ichthyosis, but not in patients with a drug-induced erythroderma. During the study period, 76.4% of the patients with psoriasis were hospitalised for the second time.

DISCUSSION

In this study, 116 cases with erythroderma were collected within a 6-year periodfrom January 2012–July 2017. The highest number of cases with erythroderma were recorded in 2014 (24.1%; n=28). Erythroderma usually occurs in the sixth decade of life, cited in prior studies by Cesar et al.,[2] Humaira T et al.,[3] Li et al.,[4] Khaled et al.,[5] Fernandes et al.,[6] and Rym BM et al.[7] The largest occurrence is reported in the sixth life decade with a male predominance.[4-8] These study results coincide with the literature regarding the gender distribution of erythrodermic patients, however it was noted that the largest occurrence of erythroderma was observed in the seventh life decade (Table 1).[2-10]

The highest total number of patients admitted were during the months of July (16.4%; n=19) and August (14.7%; n=17). This result doesn't correlate with findings by Hulmani et al.,[8] in which most of the cases of erythroderma (30.0%) were in December and January. This could be related to the underlying aetiology of erythroderma in that most cases are linked to psoriasis, which shows periods of exacerbation during the winter months. Unlike this conclusion, the result of the present study correlated with Okoduwa et al.,[11] which evidenced exposure to ultraviolet radiation and sun as an aggravating factor of erythroderma, explaining the highest frequency of cases being during the summer months of July and August.

The onset of erythroderma is gradual and insidious.[2,4,5,8,9] Cases of hypersensitivity to medications, with an unexpected onset and a faster resolution, are excluded from this definition.[2,4,5] Similar results were indicated in this study. Drug-induced erythrodermic cases were associated with a shorter hospitalisation period while the erythrodermic psoriasis cases marked the longest hospitalisation periods observed.

Of the cases, 11.2% appeared recurrently, while 29.3% appeared as emergencies. Psoriasis was the most common aetiology in both groups (76.9% and 59.0%, respectively).

The diagnostic approach of patients with erythroderma depends on their previous dermatological history.[2] Patients with a history of dermatological disorders may develop erythroderma during an exacerbation of their underlying pathology.[2] The aetiologic diagnosis is generally clear in these cases. On the contrary, final diagnosis is the result of clinical, biochemical, and histopathological findings.

As in many recent studies,[4-10] some of the clinical features observed were nonspecific. Apart from scaling and erythema that were present in all cases,[2-4,6,8,10] this study was in agreement with aforementioned analyses in highlighting pruritus as being the most common complaint from patients (100%). The same studies indicate that palmoplantar keratoderma[2,8] and changes in the nails[2,4,6,10] were present in some psoriatic patients, indicating the importance of these findings in determining the diagnosis. This is also supported by the findings of this study, where such changes were characteristic of psoriatic erythroderma.

Temperatureof 38.5°C or higher in admission was another clinical finding in 34.5% of patients, comparable to the findings reported in previous reports.[2-4,6,8,10] Temperature escalation is the result of barrier function damage, that allows the overlapping of bacterial infections, the development of secondary infections associated with hyperthermia, and thermoregulatory cutaneous function damage, all associated with body temperature disorder.

Three major changes in erythroderma were identified: increased erythrocyte sedimentation rate and C-reactive protein in the majority of the cases (93.1%), leukocytosis in approximately half of the cases (43.9%), and anaemia in a third of the cases (30.2%). These results are in accordance with César et al.,[2] Fernandes et al.,[6] and Hulmani et al.[8] (Table 2).[3,4,10]

Authors, Year, Country	Present study, 2019, Albania	César et al.,[2] 2016, Portugal	Humaira et al.,[3] 2016, Pakistan	Li et al.,[4] 2012, China	Khaled,[5] 2010, Tunisia	Fernandes et al.,[6] 2008, Brasil	Rym et al.,[7] 2005, Tunisia	Hulmani et al.,[8] 2014, India	Yuan et al.,[9] 2010, China	Akhyani et al.,[10] 2005, Iran
A										
Age group with the highest frequency (years)	61–70	71–80	50–60	50–60	50–60	50–60	50–60	60–69	N/A	N/A
Mean age of onset (years)	55.1	54.4	48.6	52.6	55.1	53.5	53.8	52.3	N/A	46.2
Male:Female ratio	1.3:1.0	1.5:1.0	1.6:1.0	3.0-1.0	1.0-1.0	1.2:1.0	2.2:1.0	14.0-1.0	2.5:1.0	1.9:1.0
B										
Number of patients	116	103	190	260	82	170	80	30	82	97
Pre-existing dermatoses (%)	78.4 (53.4% psoriasis)	65 .0(44.7% psoriasis)	65.2 (26.8% psoriasis)	69.6 (55.0% psoriasis)	43.9	58.2 (38.8% psoriasis)	72.5 (51.3% psoriasis)	63.3 (33.3% psoriasis)	68.3 (30.5% psoriasis)	59.7 (27.8% psoriasis)
Drug reaction (%)	4.3	18.4	23.7	12.7	21.9	21.8	11.3	16.6	17.0	21.6
Malignancies (%)	0.0	12.6	11.1	2.3	4.9	10.6	8.8	3.3	4.9	11.3
Idiopathic (%)	16.4	3.9	0.0	14.2	25.6	9.4	7.5	16.6	6.1	7.2

Table 1.(A) Comparing results between earlier studies with the present study regarding age groups with the highest frequency, mean onset age, and male:female ratio. (B) Comparing results between earlier studies with the present study regarding the underlying aetiology of erythroderma.

Table 2: Comparing results between earlier studies with the present study regarding clinical and laboratory findings of erythroderma.

Authors, year, country	Clinical and laboratory findings in admission
Present study, 2019, Albania	Pruritus: 116 pt, 100.0% Temperature: 40 pt, 34.5% Changes in the nails: 32 pt, 27.6% Palmoplantar keratoderma: 32 pt, 27.6% Increased ESR/CPR: 108 pt, 93.1% Anaemia: 35 pt, 30.2% Leukocytosis: 51 pt, 43.9%
César et al.,[2] 2016, Portugal	Pruritus: 100 pt, 97.1% Temperature: 56 pt, 54.4% Palmoplantar keratoderma: 52 pt, 50.5% Changes in the nails: 44 pt, 42.7% Increased ERS/CRP: 99 pt, 96.1% Anaemia: 31 pt, 30.1% Leukocytosis: 50 pt, 48.5%
Humaira et al.,[3] 2016, Pakistan	Pruritus: 97.5% Temperature: 33.6% Lymphadenopathy: 21.3% Oedema: 14.4% Hyperkeratosis: 7.2%
Li J et al.,[4] 2012, China	Pruritus: 87.7% Temperature: 40.0% Changes in nails: 29.6% Oedema: 37.7% Chills: 31.2% Lymphadenopathy: 19.2%
Fernandes et al.,[6] 2008, Brasil	Pruritus: 36 pt, 21.2% Chills: 88 pt, 51.8% Lymphadenopathy: 20 pt, 11.8% Temperature: 14 pt, 8.2% Oedema: 12 pt, 7.0% Anaemia: 49 pt, 28.8% Leukocytosis: 61 pt, 35.9% Nail changes: pitting, subungual keratosis, onycholysis, onychorrhexis: present, but not specified
Hulmani et al.,[8] 2014, India	Pruritus: 86.7% Temperature: 43.3% Shivering: 93.3% Palmoplantar keratoderma: 46.5% Anaemia: 15 pt, 50.0% Leukocytosis: 12 pt, 40.0%
Akhyani M et al.,[10] 2005, Iran	Pruritus: 94 pt, 97.5% Temperature: 32 pt, 33.6% Lymphadenopathy: 20 pt, 1.3% Oedema: 14 pt, 14.4% Hyperkeratosis: 7 pt, 7.2% Changes in nails: 31 pt, 32.6%

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

In previous studies,[2,4-10] the benefit of biopsy was variable in determining the histological diagnosis. Despite the clinical presentation of erythroderma being relatively uniform, histopathological characteristics of underlying lesions are usually distinctive.[12] In this study, cutaneous biopsy was needed to establish the final diagnosis in 86 (74.1%) of the 105 patients (90.5%) whom had cutaneous biopsy performed. This percentage is comparable to the results obtained from previous studies such as Khaled et al.,[5] with 77.0% of the cases conclusive; César et al.,[2] 66.4%; Rym et al.,[7] 74.0%; Bandyopadhyay et al.,[12] 52.0%; Kondo et al.,[13] 72.5%; and Hulmani et al.,[8] 80.0%.

The main objective of this study was to determine the underlying aetiologies of erythroderma as a manifestation of systemic and cutaneous diseases. It was evidenced that the root cause of erythroderma in 78.4% of cases was the exacerbation of pre-existing dermatoses, with psoriasis constituting the most common aetiology in 53.4% of the cases (n=62). Other present aetiologies included chronic eczema (3.4%; n=4), chronic dermatitis/spongiform dermatitis/psoriasiform dermatitis (10.3%; n=12), and subcorneal pustulosis (5.2%; n=6). The results obtained in the study correlate with previous clinical and aetiologic studies[2-10] Cases with drug hypersensitivity-induced erythroderma represented a low percentage (4.3%; n=5) compared to the results of previous studies with values that varied from 11.3–23.7%[2-10] (Table 1).

One of the most important challenges facing a dermatopathologist when evaluating skin biopsies from erythrodermic patients lies in the distinction between benign and malignant causes.[14] The ability to differentiate benign (e.g., psoriasis, dermatitis, drug-induced) and malignant (e.g., Sézary syndrome, mycosis fungoides) forms of erythroderma require immunophenotypic study of their characteristics with the use of advanced antibody panels.[15] Although clinically erythroderma is relatively uniform, immunohistochemical studies by Sigurdsson et al.[16] showed a dermal infiltration of T-helper-2 cytokines in Sézary syndrome cases compared to a dermal infiltration of T-helper-1 cytokines in benign erythroderma cases. This denotes a different underlying pathogenic mechanism.[17] In the past 10 years, new phenotypic and molecular markers of malignant Sézary cells were published, including loss of CD26 and CD7, and expression of Twist, EphA4, T-plastin, and CD158k/KIR3DL2, the latter allowing diagnosis in skin biopsies with quantitative reverse transcriptase-PCR.[18-20] In addition, among the new markers, only β-catenin and JunB have proved to be suitable for immunohistochemistry on paraffin-embedded skin biopsies.[21-24] Bellei et al. demonstrated β-catenin expression in 31% of mycosis fungoides and 70% of Sézary syndrome samples using immunohistochemistry.[14] Among new markers of CTCL, JunB is not a sensitive feature but is specific for CTCL.[14]

In reference to our immunohistochemistry findings, the percentage of malignancies, whether cutaneous or internal, was 0.0%, unlike the results obtained from the aforementioned series which indicated percentage values varying from 2.3–12.6%,[2-10] confirming the presence of malignancies such as CTCL; mycosis fungoides; Sézary Syndrome; leukaemia, nasopharyngeal, gastric, or pulmonary cancers; or histiocytosis (Table 1).

The final diagnosis of the underlying aetiology could not be determined in 16.4% of cases (n=19), classifying this group under the idiopathic/undefined category, also known as 'red man syndrome'. As the possibility of an undiagnosed CTCL was carefully considered, the nonspecific findings of histopathological examination favoured the diagnosis of idiopathic erythroderma. These idiopathic cases were found to be consistent with the reports in the aforementioned studies on erythroderma ranging between 6.1 and 16.6% (Table 1).[4-10]

Regarding the systemic disease group, no case with erythroderma as a manifestation of internal diseases was found. The data discussed in the above paragraphs show variations in relative percentages of different aetiologic and ethnic groups of erythroderma. These changes may be related to genetic, geographic, and social characteristics of patients with erythroderma.

It is important to understand the gravity of erythroderma. Although this condition is relatively rare, it has a significant mortality rate which is reported in several studies: Khaled et al.[5] reported a mortality rate of 1.3 per 1,000 patients per year; Li et al.,[4] reported a mortality percentage of 3.2%; and César et al.,[2] reported a mortality percentage of 5.8%. In this study, no fatal case was detected

(mortality: 0%). This value only corresponds to the hospitalisation days of erythrodermic patients, as it does not include follow-up data.

This study provides important information on the characteristics of erythroderma in the authors' country, due to the importance of this pathology and the risk it may cause to the patient's life. A limitation of the study is the limited number of patients considered. Regardless of this, these findings finally create a base of development for further studies and research into this condition.

CONCLUSIONS

Erythroderma is a challenging condition with difficult diagnosis and reserved prognosis.

This study revealed a high percentage of secondary erythroderma with a pre-existing dermatosis, where psoriasis was the predominant aetiology and there was a relatively low percentage of primary erythroderma. Most of the clinical features and laboratory abnormalities were identical, irrespective of the aetiology. Histopathological examination was the most helpful tool for concluding the diagnosis, yielding a positive clinical correlation in the majority of cases. When no underling cause is found, careful follow-up is recommended.

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A Review of Primary Immune Deficiency Disorders

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Disclosure: The authors have declared no conflicts of interest.

Received: 04.03.20

Accepted: 14.05.20

Keywords: Agammaglobulinemia, B cell deficiency, hypogammaglobulinemia, innate immune deficiency, newborn screening (NBS), primary immunodeficiency disorders (PIDD), T cell deficiency.

Citation: EMJ Allergy Immunol. 2020;5[1]:70-77.

Abstract

This scenario-based review of primary immunodeficiency diseases (PIDD) discusses the differential diagnosis, usual presentations, work-up, and treatment of children with the most commonly encountered immune disorders. Newborn screening (NBS) for severe combined immunodeficiency (SCID) is covered, as are later presenting disorders caused by B cell defects and disorders of the innate immune system.

INTRODUCTION

Primary immunodeficiency diseases (PIDD) can broadly be described as a group of various defects of the immune system which lead to a variable clinical picture of immune dysregulation.[1] The clinical picture present depends upon the specific immune deficiency, but may involve some combination of recurrent infections, autoimmunity, atopy, lymphoproliferative disorders, or malignancy. Prevalence of PIDD is variable depending on the specific immune deficiency; studies performed in Korea, Sweden, Taiwan, South Africa, and Singapore all found primary antibody deficiencies to be most common, followed by defects in phagocytosis.[1]

Because these diseases are very rare, diagnosing them can be difficult and late diagnosis can lead to a worse prognosis and a delay in life-saving treatment. Further, the same genetic defect can have different manifestations of the disease.[2] Diagnosis thus requires a thorough knowledge of patient history, a physical exam, and appropriate laboratory tests (which can be nonspecific). There are several guidelines in place to help physicians make a proper diagnosis, such as the Jeffrey Modell Foundation[3] and the American Academy of Allergy, Asthma, and Immunology.[4]

Given the complexity of PIDD, this review provides a scenario-based review of the major PIDD, stating common presenting symptoms, a differential diagnosis, laboratory tests, and the treatment and management of the most common PIDD.

SCENARIO ONE

Eli is 9 months-old and has a "constant cold." He has had thick nasal discharge for 2 months and two ear infections that have required antibiotics in

the last 3 months. He has never been hospitalised. There is no family history of PIDD and his 2-year-old sibling is healthy. Eli was born full-term, and newborn T cell receptor excision circle (TREC) screening for severe combined immunodeficiency (SCID) was normal. He was born at the 50th percentile and is now at the 10th percentile.

B-cell defects or deficiencies may manifest at this age as maternal antibodies are waning. The usual transplacental transfer of maternal IgG occurs during the third trimester. A preterm baby may not have received all the usual IgG, but this full-term baby would have received maternal IgG and should have been making his own at this time.

Transient hypogammaglobulinemia of infancy (THI) is commonly identified in the first year of life but some infants have low IgG until they are several years old. Total Ig is low but specific antibodies are present.[5] Historically this has been considered a normal variant and some increased incidence of infection may be because of THI or it may be coincidental.[1,2] THI is a diagnosis of exclusion.[6]

Selective serum IgA deficiency is relatively common in children and adults. The estimated prevalence is between one in 200 and one in 1,000.[7,8] IgA deficiency is typically asymptomatic but can present with recurrent respiratory infections from encapsulated organisms and gastrointestinal infection and, although it is controversial, there may by an increased incidence of reaction to blood transfusions because of IgG antibodies targeting IgA.[9] Selective IgA is thought to be symptomatic only in individuals who cannot make mucosal IgA.[9]

IgA may be the first Ig class to fall in the development of common variable immunodeficiency (CVID). IgA deficient patients are, therefore, usually periodically screened for progression to CVID. Typically, diagnosis of IgA deficiency is made after the fourth year of life and requires that other causes of hypogammaglobulinemia and T-cell defects be excluded.[9] Eli was 9 months-old and the absence of IgA would still be physiologic.

CVID is a primary immunodeficiency that usually presents in the second or third decade of life with increased infections. The estimated prevalence is one in 20,000 to one in 50,000.[10,11] CVID can also present with noninfectious sequelae, such as autoimmune disease.[10,12,13] It is a heterozygous disease affecting B cells.[14] The most commonly known defects are mutations in the transmembrane activator and calcium modulator, the inducible costimulator receptor, and some defects of the cluster of differentiation (CD)-19 molecule.[8,11] These defects all affect late B-cell function, and patients with CVID typically have normal total B cells, but many will have low memory B cells ($CD19^+CD27^+IgM^-$).[14] CVID cannot be diagnosed before the age of 4 years and can only be diagnosed after other identifiable causes of hypogammaglobinemia have been excluded.[11,15] According to the diagnostic criteria there should also be a two-standard deviation decrease of IgG and either IgM or IgA and an inability to make specific antibodies.[11,15]

Agammaglobulinemia, which is most often caused by a mutation in the Bruton's tyrosine kinase gene (BTK), typically presents at around 6-9 months of age when maternal antibody levels decline, and the infant fails to produce antibodies.[16,17] Recurrent respiratory infections because of encapsulated bacteria, such as *Streptococcus pneumoniae* and *Haemophilus influenzae* Type B, are the most common infections.[2,11,17] Definitive diagnosis requires the presence of hypogammaglobinemia or agammaglobulinemia and <2% $CD19^+$ B cells in the peripheral blood. X-linked agammaglobulinemia (XLA) can also be confirmed by the absence of the *BTK* gene.[11]

Mutations in other genes involved in the development of the early B cell can also cause agammaglobulinemia.[18] These genes include the μ heavy chain gene (*IGHM*), λ5 (*IGLL1*), Igα (*CD79A*), Igβ (*CD79B*), and *BLNK*.[9,16] The autosomal recessive mutations result in a clinical picture similar to XLA.

The absence of tonsils has been an important finding in XLA research and sometimes aids diagnosis.[9,18] Eli presented with recurrent upper respiratory infections and recurrent sinusitis, but cases of meningitis, osteomyelitis, and septicaemia because of encapsulated bacteria are common infections, especially in untreated agammaglobulinemia.[2,11,19] Patients can also be at risk for chronic diarrhoea because of *Campylobacter jejuni* and *Giardia lamblia* infection.[2,11,19] Because agammaglobulinemia patients have a functional T-cell system,

most viral infections are cleared without any difficulty. However, they are susceptible to enterovirus infection and when the oral poliovirus vaccine was in common usage, it could cause meningoencephalitis in individuals with undiagnosed agammaglobulinemia.[2,11]

Increased autoimmunity can be seen in patients with XLA but has typically been thought to occur at a lower frequency compared to other primary immunodeficiencies.[20] Patients with agammaglobulinemia have a higher rate of inflammatory conditions such as rheumatoid arthritis or Crohn's disease than the general population.[20]

Some patients present later than the classic 6–9 months because of liberal use of antibiotics for less severe infections. It is important not to dismiss the diagnosis in older children before investigation. It is also important to be aware of XLA cases reported with, what used to be classified as "hypo IgM," normal IgG and IgA but poor specific antibody formation.[21]

Treatment of XLA involves lifetime replacement of Ig intravenously or subcutaneously.[2,11] Standard dosing requires an initial dose of 400 mg/kg every 3–4 weeks and subsequent dosing individualised to the patient as determined by IgG levels. The goal of treatment is to minimise infections. Aggressive antibiotic therapy needs to be initiated when any infection is suspected.[2,11] Haematopoietic stem cell transplant (HSCT) is not routinely recommended for patients with XLA, despite the wide use in other PIDD, because intravenous IG therapy is so successful and the limited studies on the efficacy of HSCT do not support its use for agammaglobulinemia.[2,11]

Complete blood count with differential and IgG, IgA, and IgM are sent. He has an IgA level <7 mg/dL, an IgG of 107 mg/dL (lower-limit of normal for this age is 217 mg/dL), and IgM is undetectable. On examination it is noted that there is no tonsillar tissue present. Lymphocyte enumeration is ordered. Eli has no CD19 B cells. Genetic testing confirms a defect in Bruton's tyrosine kinase which stops maturation of B cells. Eli will have an excellent prognosis if treatment is begun as soon as possible.

SCENARIO TWO

Michael is 6 days old and was born full-term via vaginal delivery to a healthy mother with no perinatal complications or prenatal illnesses. He is breastfeeding well. His parents receive a phone call that NBS for SCID is positive. They are asked to bring him to the immunologist office at the local university health centre.

NBS for SCID detects TREC, circular DNA remnants that are byproducts of newly formed naive T cells.[22] The TREC assay was piloted in 2008 in Wisconsin[23] and is now utilised for NBS throughout the USA and in some other countries.[24,25]

Most positive TREC screens are from preterm infants who are not yet making competent T cells because of prematurity and/or illness. Some infants have a transient T-cell lymphopenia and severe illnesses not associated with PIDD, which may result in low T cells.[24,25]

DiGeorge syndrome (DGS), most often because of *22q11.2* chromosomal deletion, is a common cause of a positive TREC. DGS varies and can affect not only the immune system but also cause facial anomalies, cardiac defects, and parathyroid abnormalities. Complete DGS renders the infant with essentially no T cells because of a lack of the thymic tissue necessary for negative and positive selection of T cells for maturation.[26] Although chest X-ray may be utilised to evaluate for thymic tissue ('sail sign' or thymic shadow), it is not a reliable tool for diagnosis because thymic tissue may be very small or in an ectopic location.[26] Flow cytometry for T-cell markers is more reliable than a chest X-ray and less invasive than a CT scan for verification of a functioning thymus. Flow cytometry is utilised to enumerate $CD3^+$ T cells in circulation. Mitogen proliferation, especially to phytohemagglutinin (PHA), is utilised to determine if the T cells present are functional.[26]

The preferred treatment for complete DGS is thymic transplant, with survival rates of 58–75%.[26] Thymic transplant is not readily available for most patients as it is approved at only a few centres. DGS patients most often have other conditions that must be treated prior to transplant, most commonly unstable congenital heart disease.

Partial DGS, or incomplete DGS, can also trigger a positive TREC in infants with low but functioning T cells. Recovery of adequate T-cell numbers occurs over time. There is evidence that patients with incomplete DGS are more likely than the general population to develop autoimmune disease later in life, and it is advisable to monitor these individuals.[27]

PIDD other than SCID that have variably low T cells, such as ataxia-telangiectasia or even hypomorphic forms of SCID, may trigger a low TREC.[28] Omenn syndrome, which is sometimes associated with a heterozygous defect in the rearrangement of the recombination-activating gene (RAG), was often difficult to diagnose before TREC NBS because the infants had a severe eczematous rash, lymphadenopathy, eosinophilia, hepatosplenomegaly, and T and B cells that are present but nonfunctioning, which are now identified by NBS.[28]

Infants with a positive TREC are evaluated to determine the etiology of the low T cells and to determine if the cause is SCID. The morbidity and mortality for SCID transplant is decreased if performed prior to 3 months of age, and prior to any infectious complications of SCID.[29] Flow cytometry is used to further delineate the number of T-, B-, and natural killer (NK)-lymphocytes in infants with a low TREC.[30]

Michael's exam reveals a healthy appearing 6-day-old boy with no heart murmur. Family history is negative for PIDD and Michael has no siblings. Laboratory testing is ordered for lymphocyte enumeration and mitogen proliferation. Blood is drawn and held for genetic screening. Breastfeeding is discussed and the mother's cytomegalovirus (CMV) IgG and PCR are sent to the lab.

If flow cytometry supports SCID there are precautions that should be taken for the infant such as protective isolation. Hospitalisation is encouraged by some, but infants can be at home under strict precautions if hospitalisation is not practical. When considering whether or not to hospitalise the infant prior to transplant, it is important to determine if there are other young children in the home and if the parents are able to strictly supervise the infant until definitive treatment of stem cell or bone marrow transplant can be done.

The infant with SCID will not be able to respond to vaccines and will be started on replacement Ig as maternal antibodies wane. They should not receive vaccines, especially live vaccines which may do harm. Other persons in the home should receive the influenza vaccine to avoid endangering the infant.[31]

All mothers should be counselled to stop breastfeeding until their CMV IgG and IgM serology is known. It is controversial to advise breastfeeding if the mother has CMV negative titers. Some would argue that the mother may develop CMV. Viral infections, in particular CMV, remain the most common cause of death for infants with SCID. If mothers are seropositive, they should avoid breastfeeding entirely and the infant should have a CMV PCR performed weekly.[31,32]

There are several measures of prophylaxis for infants with SCID. Ig replacement should be started when maternal antibodies wane. Trimethoprim-sulfamethoxazole for *Pneumocystis jiroveci* pneumonia prophylaxis after all neonatal jaundice is cleared, fluconazole for fungal prophylaxis, and acyclovir for prophylaxis of herpesvirus should be administered. Palivizumab may be given during the respiratory syncytial virus season. If blood products are needed they should be irradiated, leukocyte depleted, and CMV negative.[30]

In a study conducted after initiation of NBS, 19% of infants with SCID had X-linked SCID, but this type was previously reported to be approximately half of all cases. The same report revealed that other types of SCID are more common than previously believed, and the incidence of SCID is overall much higher than previously reported.[24] The less prevalent types of SCID were apparently missed prior to the start of routine screening.[24,25]

X-linked SCID is caused by defects in the common γ-chain of the IL receptor. Mutations in this gene result in absent T and NK cells. These patients have the typical SCID phenotype, with presentation in the newborn period characterised by recurrent severe infections, chronic diarrhoea, and failure to thrive if not diagnosed via NBS.[32,33]

Janus kinase-3 (JAK3) deficiency is the other $T^-B^+NK^-$-SCID, but it is inherited in an autosomal recessive fashion. JAK3 encodes for a tyrosine kinase that is coupled to cytokine receptors that are essential for lymphoid cell development.

This deficiency is virtually indistinguishable from X-linked SCID, with the exception that females could be affected.[32]

If flow cytometry shows absent T, B, and NK cells, suspicion for adenosine deaminase deficiency (ADA) increases. ADA-deficient SCID accounts for 10–15% of all cases.[28] ADA-SCID is a purine metabolism disorder that kills lymphocytes by build-up of toxic metabolites. It affects the immune system but is not a genetic defect intrinsic to the immune system.[30] This type of SCID is usually diagnosed in infancy but 15–20% are diagnosed later in life as infections occur. ADA can be missed on NBS if lymphocyte counts have not yet fallen when the NBS card is collected, which has prompted some states to add ADA enzyme screening to NBS.

SCID that is T- and B-cell negative may be caused by *RAG1* and *2* deficiency. RAG are expressed by lymphocytes and help to mediate double strand DNA breakage at recombination sites.[28,32,33] Inherited in an autosomal recessive pattern, RAG deficiency is one of the defects that can also cause Omenn syndrome. It is sometimes missed prior to NBS for SCID because there are often lymphocytes present which may be of maternal origin or clonally expanded T cells of infant origin that are poorly functioning.[33] RAG defects can also cause leaky SCID, a less severe form of SCID that is characterised by low, but not absent, T cells.[33,34]

There are now >50 genetic defects associated with SCID. Genetic testing is important because of preparation for bone marrow transplant or stem cell transplant, especially if the defect is in the DNA repair genes.[32,35] If there is a trial open for genetic therapy for the type of SCID identified, the family may opt to apply for that therapy, which may go on to become standard of care in the near future.[36]

The laboratory results reveal normal absolute count of B cells, but nearly absent $CD3^+$ T cells and absent $CD3^-CD56^+CD16^+$ NK cells. The few T cells present are predominantly $CD45RO^+$, indicating memory cells of maternal origin. Mitogen proliferation to PHA is very low. The genetic screen for this patient is positive for JAK3 deficiency. Gene therapy for JAK3 deficiencies are currently being researched, but no trial is open to this family. Testing is initiated for human leukocyte antigen-matching for bone marrow transplant or stem cell transplant.

SCENARIO THREE

Hallie is 3 years old and her mother is concerned about mannose binding lectin deficiency (MBL-D), an immune problem that she read about on the internet. Hallie had an abscess in her nappy area about 1 year ago that required drainage and intravenous antibiotic. Her mother believes they told her it was a methicillin-resistant Staphylococcus aureus (MRSA) infection. She has also had several skin abscesses requiring oral antibiotic. She has not had other infections and there is no family history of PIDD. Her umbilical stump separated at 1 week of age. Dentition appears normal. Before lab results are available Hallie develops a fever of 103° Fahrenheit and shortness of breath and is hospitalised. Physical exam reveals a respiratory rate of 50, hypoxia, and crepitations in the right posterior lung field. A chest X-ray reveals a right lower lobe pneumonia. She is started on antibiotics to cover pneumococcus and community acquired pneumonia.

The complement system is part of the innate immune system, although the classical complement pathway is primarily activated by antigen-antibody complexes. The alternate pathway's main trigger is bacterial endotoxin. Some components of yeast cell wall and mold, typically *Aspergillus*, also trigger the alternate pathway. The lectin pathway is activated when lectin recognises carbohydrate residues on bacteria and activates the complement system by binding to MBL. *Neisseria* and *Salmonella* or yeast are most commonly recognised by MBL. All three complement pathways promote lysis, opsonisation, and phagocytosis of bacteria.[37,38]

Primary complement deficiencies can lead to increased infections and autoimmune disease. C2 component deficiency is one of the most common complement disorders. It can be asymptomatic or can present with sinopulmonary infections or bacterial meningitis. About 10% of patients with C2 deficiency will have autoimmune disease, most commonly lupus erythematosus.[39] Terminal complement component deficiencies leave patients prone to *Neisseria* meningitis.[39] Deficiencies have

been described in C3 and C4 components of complement, and these may present as infection or autoimmune disease. Most complement deficiencies are autosomal recessive, but Properdin deficiency, an alternate pathway deficiency, is X-linked and results in susceptibility to fulminant meningococcal infections.[40]

Complement disorders other than MLB-D are rare. MBL-D affects 5–10% of the population and is usually asymptomatic.[41] If MBL-D is present with another condition, such as cystic fibrosis or HIV, it can hasten the primary disease progression or susceptibility.[42,43] It is controversial whether the defect/deficiency alone can lead to increased infections, but patients with no other disorder than MBL-D have been reported to have increased infections.

There are many secondary causes of staphylococcal abscesses of the skin (e.g., chronic skin conditions such as atopic dermatitis, burns, and trauma). Some PIDD are characterised by presentation with staphylococcal abscesses. Autosomal dominant hyper IgE syndrome is a deficiency of signal transducer and activator of transcription-3 (STAT3), and affects many systems including skin, skeletal, and immune systems. The disorder was characterised long before the genetic defect was discovered but this has allowed earlier recognition of the disease.[44,45] Patients typically have high serum IgE, elevated eosinophils, frequent fractures and skeletal anomalies, eczematous skin, and frequent staphylococcal and fungal infections. The abscesses are usually deep without active neutrophils. Neutrophil chemotaxis is often poor in patients with STAT3 deficiency. The abscesses must be drained before they are flocculent, and awareness of this issue is key to decreasing morbidity and mortality.[46] A multisystem scorecard is utilised for initial diagnosis of STAT3 deficiency, and genetic testing confirms the diagnosis.[47] This patient does not have a high score on the initial evaluation but gets extra points for young age because symptoms worsen with time.

Leukocyte adhesion deficiency (LAD) is another PIDD that can lead to staphylococcal abscesses. LAD is rare and there are several subtypes, all autosomal recessive in inheritance, which lead to increased abscess formation. In the most common subtype, LADI, the neutrophils can exit the bone marrow and reach the circulation but lack the CD18 (β-2 integrin-chain) function necessary for extravasation to infected tissues.[48-50] Patients have a poor ability to form abscesses. Patients with severe LADI often have late umbilical cord separation, omphalitis, and severe periodontal disease.[48,51] With moderate-to-severe LADI, leukocyte counts are elevated because of the inability to extravasate.[48] There is variability of LADI with extreme severe disease presenting in the first weeks of life. Without early intervention of stem cell or bone marrow transplant mortality is high, but some children with less severe disease present in later childhood.[48,52] Flow cytometry is utilised to detect CD18 on leukocytes.[50]

LADII, a glycosylation disorder, is characterised by cognitive deficiency and severe growth failure.[53,54] LADIII, an integrin activating protein disorder, is associated with a severe bleeding disorder caused by platelet dysfunction.[55] Neither LADII or LADIII seem likely in Hallie's case.

Chronic granulomatous disease (CGD) is a disorder of the NADPH oxidase system which usually forms hydrogen peroxide (H_2O_2) and reactive chloride species.[56,57] Patients are prone to infection with catalase positive organisms such as *Staphylococcus*, *Serratia*, and *Aspergillus*.[58,59] NADPH oxidase is formed of multiple subunits and there are several known defects in these subunits, the most common being a defect in the gp91 phox unit, which is an X-linked mutation. Some female carriers of this mutation have later onset and less severe disease. The autosomal recessive forms lead to the same types of infection. Patients with CGD may also suffer from granulomas that are thought to be secondary to chronic inflammation, which may cause organ obstructions and chronic pain.[59,60]

The most accurate assay for the diagnosis of CGD involves measurement of hydrogen peroxide in phagocytes by dihydrorhodamine reductase. The assay is performed by flow cytometry. Genetic testing for some X-linked and autosomal recessive forms is available.[61]

Her immunology labs return. IgG, IgA, IgM, and IgE are all within normal limits for her age. Her lymphocytes subsets are within normal range by percentage and by absolute counts. Her recall antibodies to pneumococcal and tetanus are

protective. Her CH50 is 95% (normal), and her mannose binding lectin is normal. Her oxidative burst by dihydrorhodamine assay is very low, showing a population of granulocytes that do not stimulate and have poor oxidative burst. Antibiotic coverage is changed to include Staphylococcus.

Morbidity and mortality of CGD has improved significantly since studies supporting that staphylococcal prophylaxis treated with trimethoprim-sulfamethoxazole and fungal prophylaxis treated with itraconazole are of benefit.[62,63] Shortly before the antimicrobial prophylaxis studies were released, interferon-γ was shown to be of benefit in decreasing infection but has exhibited controversial benefit when paired with prophylaxis.[59,64,65] Bone marrow or stem cell transplant remains a possibility for CGD patients, particularly those with severe recurrent infection, and gene therapy trials for X-linked CGD is under investigation.[11]

The pneumonia improves and she is placed on staphylococcal prophylaxis as well as fungal prophylaxis prior to discharge. Discussion of possible use of interferon-γ is also presented to the family. Genetic testing is sent to verify the type of autosomal recessive CGD.

CONCLUSION

NBS for SCID now helps identify many severe immune deficiency cases early in life, but providers must still be vigilant for signs and symptoms of PIDD such as infections, autoimmune disease, and failure to thrive. Family history of PIDD is always an indication to investigate for PIDD. As time goes by more defects of the immune system, either humoral, cellular, or innate, are appreciated and defined.

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A Qualitative Enquiry into the Lived Experiences of Adults with Atopic Dermatitis

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Disclosure: The authors have declared no conflicts of interest.

Received: 24.04.20

Accepted: 16.06.20

Keywords: Atopic dermatitis (AD), atopic eczema, psychodermatology, qualitative, quality of life (QoL).

Citation: EMJ Allergy Immunol. 2020;5[1]:78-84.

Abstract

Background: atopic dermatitis (AD) has been related to poorer health-related quality of life (HRQoL) in adults and there is lack of qualitative research that explores how this long-term condition affects the lives of adults. The purpose of this study was to explore the impact of AD on the HRQoL of adults through semi-structured interviews.

Study design: this was a qualitative study using semi-structured interviews.

Methods: adults with a clinical diagnosis of AD were recruited by advertising on a university campus and through social media sites. All participants completed a screening questionnaire on AD diagnosis, treatment, duration, and severity. Semi-structured interviews were conducted either face-to-face or on the telephone then audio-taped, transcribed verbatim, and analysed using thematic analysis.

Results: the study group (n=19) consisted of 10 White and nine Black and ethnic minority participants, aged 19–52, of whom 18 were female. Three superordinate themes emerged from the analysis: 1) visibility of AD; 2) threats to inner sense of self; and 3) contrasting reactions and support from others. There were qualitative differences in the narratives of those who were diagnosed with AD at an early age compared to a later age, and across ethnic groups.

Conclusions: AD has a great impact on the QoL of adults. Participants in this study discussed issues that have not been reported in quantitative research, particularly around the lack of understanding of the psychological impact of AD and the stigma attached to it. Consideration of these factors may enhance disease management and improve HRQoL. Understanding and recognition of AD as a complex long-term condition involving significant psychosocial impact is crucial. The findings from this study suggest more integrated and accessible psychological support is required for people with AD. Males were under-represented in this study, and further exploration of the impact on AD in males is needed.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease characterised by intense pruritus (itch), erythematous lesions, increased water loss through the skin, and xerosis (dry skin). The lifetime prevalence of AD is 10–20% in children and 1–3% in adults worldwide; 85% of affected children develop the disease before the age of 5 years.[1,2] Although the condition resolves in many during childhood, AD may persist into or manifest for the first time in adulthood.[3] Less than one-half of patients with AD have complete resolution by 7 years of age, and only 60% of them have resolution by adulthood, indicating the chronic nature of AD.[4]

Importantly, in several studies, subjective experience of AD was a more powerful determinant of quality of life (QoL) than the degree of objective severity, indicated by the area of affected sites.[5] However, these measures do not enable us to encapsulate, summarise, and effectively convey the full-life impact of the experience of AD. Existing QoL measures rely on limited questions concerning daily life experience during the day, week, or month preceding the assessment. The vast majority of research assessing QoL in adults is quantitative and much is cross-sectional, thus very little is known about the experience of adults living with AD. The aim of this study was to understand participants' experiences of living with AD using semi-structured interviews.

METHODS

Study Design and Setting

This was a qualitative study using semi-structured interviews conducted with adults with AD. The study received ethical approval from the University Research Ethics Committee. Inclusion criteria for this study were adults aged 18 or above with clinically diagnosed AD and consent to take part in the study. The exclusion criteria for the study were participants living outside the UK.

Participants and Recruitment

Participants were identified through advertising of the study at a large UK university and via social media platforms such as Facebook and Twitter. A total of 19 participants were recruited; four were identified through the university, five were identified through word of mouth and snowballing techniques, and 10 were identified through social media.

Participants consisted of one male and 18 females, with a mean age of 34 years (age range: 19–52). All participants had concomitant conditions. Ten participants were White British, six were Indian British, and three were Pakistani British. Disease duration ranged from 7 to 50 years. Fifteen participants were being treated by a dermatologist, and seven participants had a family history of AD. Current medication taken by participants included topical corticosteroids, oral immunosuppressants, antihistamines, and over-the-counter creams and ointments. Patient-assessed severity was explored using a non-validated visual analogue scale (Table 1).

Data Collection

The authors developed an interview schedule led by the second author, drawing upon the findings of a systematic review on the impact of AD on QoL.[6] Issues such as sleep, employment, and physical activity, which are commonly found to be disrupted in those with AD, were also explored. Questions were prepared and formatted in a manner that allowed participants to discuss in as much depth about their experiences as possible because the intention was to allow for an exploration of their experience without drawing upon any pre-existing theories. Participants' experiences of living with AD on a daily basis in general, their relationships with significant others, their experiences with treatment and management of the condition, as well as physical and psychological implications of living with AD were explored. The first author conducted all of the interviews. Questions were framed in an open-ended manner, asking participants to "tell me a bit about your diagnosis of AD," then slowly moving to more sensitive topics such as "how has AD affected your relationships?" once a rapport between the participant and researcher had been established. The interviews were either conducted face-to-face or over the telephone, then audio-recorded and transcribed verbatim.

Data Analysis

Interview data were analysed thematically, recognising the interaction between the

researcher and the data. Thematic analysis has six clearly defined steps: 1) familiarisation with the data; 2) generation of initial codes; 3) searching for themes; 4) reviewing themes; 5) defining and naming themes; 6) and producing the report.[7]

RESULTS

Three superordinate themes were developed from the analysis of the interviews: 1) experiencing threats to inner sense of self; 2) living with the visibility of AD; and 3) contrasting reactions and support from others.

Experiencing Threats to Inner Sense of Self

The two aspects to this superordinate theme involved the various emotions that participants with AD discussed experiencing as a result of their condition and issues with self-consciousness.

Experiencing intermittent heightened emotional distress emerged as an important theme. Although some participants identified feeling "happy" some of the time, the majority also experienced periods of intense emotional distress that they attributed largely to the unpredictability of their condition and loss of control over their flares. Narratives were punctuated with words that powerfully identified their emotive experience: "worry," "fear," "anger," "pain," "sadness," "depression," "frustration," "horrible," and "embarrassment." Worry or fear (associated with flares); sadness, dysphoria, or depression; and anger and frustration were also connected to AD, and therefore appraised as emanating from the experience of having flares and suffering with the condition for such a long duration. This sense of frustration was closely linked to uncertainty surrounding the allergens and triggers. Participant 5 describes "drowning" in her own misery when she gets a flare-up.

Table 1: Participant characteristics.

Participant	Age (years)	Ethnicity	AD duration (years)	Concomitant conditions	Patient-assessed severity	Family history (Y/N)
1	27	Indian British	27	Food allergy, hay fever	8/10	Y
2	44	Pakistani British	42	Allergy	8/10	N
3	26	Indian British	8	Food allergy	7/10	Y
4	32	White British	30	Hay fever	8/10	Y
5	38	Indian British	17	Asthma	6/10	N
6	34	White British	34	Food allergy, hay fever	5/10	N
7	47	White British	46	Asthma	7/10	Y
8	43	White British	43	Food allergy	6/10	N
9	31	White British	27	Asthma	7/10	N
10	25	Indian British	25	Food allergy	5/10	N
11	37	White British	36	Asthma, food allergy	8/10	N
12	19	Pakistani British	19	Food allergy	6/10	N
13	48	White British	42	Asthma, hay fever	7/10	Y
14	52	White British	48	Food allergy	5/10	N
15	34	White British	32	Hay fever	8/10	Y
16	28	Indian British	25	Food allergy, hay fever	7/0	N
17	28	Pakistani British	28	Asthma, hay fever	8/10	N
18	19	White British	19	Asthma, food allergy	7/10	N
19	29	Indian British	27	Hay fever	4/10	Y

AD: atopic dermatitis; N: no; Y: yes.

Participant 5: "At that point I was just like, I'm not going to do any work, I'm not going to go to college when I'm like this, I'm just going to sit here and just going to drown in my own misery. [sic]"

Living with a long-term condition such as AD often resulted in an altered view of self. A few participants discussed that their condition had become such a strong part of themselves that they could not imagine life without AD, with Participant 18 describing it as a "constant presence" whereby she could not imagine not being "itchy every day." Participants reported that AD was responsible for unsightly physical appearance and this often resulted in them conveying various emotions, especially during times when their AD was more severe and prevalent on areas of the body visible to others. Periods of uncontrolled AD were characterised by low mood for some participants. Some used emotive language to describe how they felt about periods of uncontrolled AD. Participants described their mood using words such as "snappy" and "hot-headed" in times of flare-ups. Participant 6 cited her mood as being so low that she stayed confined to her room for days. Many participants also discussed the degree to which their condition threatened their sense of self. The tone of some of the narratives reflected an underlying desire to be "normal," and a steadfast belief that if their AD were to be cured, it would confer on them a state of normalcy. It reflected their hope for an idealised "normal" self.

Participant 12 described that due to her religion she covered up her skin, but was doubtful of whether she would have the confidence to allow the affected skin to be visible to others because she felt that people within her community would judge as a result of a lack of understanding. Similarly, Participant 17 explained that when she visits Pakistan, she feels more judged and less confident than in the UK, where she believes people are more educated about AD. Many participants also reported feeling bad-tempered, down, depressed, and less tolerant when they had flares. In fact, four participants described being diagnosed with clinical depression as a direct result of their AD. Participant 3 had extensive facial scarring from his AD, which resulted in severe clinical depression, suicidal thoughts, and social withdrawal.

Participant 3: "My skin was so bad on my face that I didn't want to laugh like it hurt to laugh or smile as well, yeah it did affect my mood a lot when my skin was really bad I was always alone I always wanted to be by myself. [sic]"

Living With the Visibility of Atopic Dermatitis

Most participants were dissatisfied with the appearance of their AD. They felt that their AD looked unsightly and consequently perceived themselves as abnormal. Their scars, pigmentation, and inflammation acted as a constant reminder to the participants and others of their continued suffering. Many felt stigmatised by their condition, particularly when their AD was prevalent on visible areas such as the face, neck, and arms. They believed that others would judge them as having other conditions, such as AD of the scalp being mistaken for hair lice, or their condition being contagious. They appeared to care deeply about what others thought of their AD and strived to keep it hidden so as not to raise any questions or thoughts; Participant 8 explains in the following excerpt about her fear of what others thought of her condition.

Participant 8: "I'd be worried about, you know, whether they were looking at it, I would be looking at them trying to see if they were, their eyes were, you know, sort of drawn to my eczema. I try my very, very best not to let my hands wander and start scratching. So, you know, I try to be aware, you know; a bit more vigilant if I was meeting somebody new. [sic]"

Many participants also felt extremely self-conscious of their condition, to the point that they felt the need to conceal their condition (e.g., wearing long sleeves, covering their legs and feet, wearing corrective foundation on areas with scarring/pigmentation).

Feeling self-conscious in relation to their AD resulted in participants adapting their behaviour in ways to "hide" their AD, such as not liking to see their reflection in the mirror or having their photographs taken. Participants also discussed how their AD made them look "ugly" or "horrible," with Participant 8 explaining that as a result of having AD on her hands, she felt compelled to hide her hands when shaking hands with others by flipping down the back of her hand. Participant 2 also explains in the following extract how AD

has affected her body image, and this is primarily a result of postinflammatory pigmentation, which is a common outcome of severe AD. Similar to Participant 2, other participants also felt vulnerable when exposing their condition to the world.

Participant 2: "I have got pigmentation all over, I have got discoloration, I don't go out without my foundations. Um, it makes me feel really conscious, especially when you're talking. I would not be able to talk, sit across, and then speak with somebody eye to eye contact. [sic]"

Contrasting Reactions and Support From Others

When discussing healthcare professionals (HCP), the majority of participants passionately felt that their general practitioners (GP) and primary care doctors did not understand the psychological impact of AD on them, and that there was a general idea amongst participants that GP were not equipped to address and treat mental health issues that arose as a result of AD. Family and friends were a central part of participants' support network, and many felt that those who knew them for the longest and those who had AD understood the participants' situations best.

Dismissed by Healthcare Professionals

When exploring perceptions of the care received from GP, most participants reported that GP did not provide adequate information on the condition itself, its aetiology, or prognosis. One participant also felt that healthcare was centred around children and not enough attention or resources were available or dedicated to the adult population.

Several participants expressed having to "push" for further tests or referrals after they presented to their GP with worsening symptoms. Relationships between participants and their doctors were complex. Participants felt that expertise in skin disease varied between GP. Participants reported that GP were sometimes dismissive of the seriousness of their condition. Participants also felt that this attitude reflected either the lack of experience and interest in the area by the GP, or a lack of appreciation of the psychological impact of AD. Participant 18 described never being referred to a mental health professional despite being diagnosed with clinical depression and anxiety and having asked two or three times to be referred to a "proper mental health doctor" and not an unspecialised nurse. She discussed how it would be ideal to have one person who is specialised in her AD and mental health.

For some participants, pejorative or unsympathetic attitudes of their GP contributed to feelings of guilt or decreased self-esteem; however, not all negative experiences with GP were necessarily a 'failing' on the doctor's part. Participants appreciated the difficult nature of skin disease management, and the demands on GP and their responsibilities were also acknowledged by many. The fact the AD is not life-threatening was a key factor in the disease being trivialised by HCP.

A few participants expressed disbelief that a "simple condition" such as AD does not yet have a cure, and how it is not possible with medical "technology being so advanced" that there was no known cure for the condition. A few participants appeared to relate the lack of cure for AD with the limited knowledge of GP and a lack of knowledge and education of the general public regarding AD. With regard to HCP, numerous participants eluded that they provided better care when it came to their condition than their GP, and often took it in their own hands to alleviate flare-ups and educate others of the condition rather than seeking medical help.

Family and Friends

Participants stated that they did not generally engage in speaking about the impact of their condition to friends and family because they do not want to be perceived in a negative light; many had anxieties that it reflected a sign of weakness. Participants of South Asian background were particularly reticent about talking about their condition to others for this reason. For example, Participant 17 discussed that as a result of her family being "conservative," she did not feel that she could discuss her condition openly with them; similarly, Participant 17 also perceived a lack of education about AD in her family and relatives and therefore chose not to talk about her condition openly. The majority of participants, however, described feeling supported by their parents and siblings, especially in circumstances

in which their family members had a history of AD. While many participants reported strangers viewing their condition as contagious, most felt that this was not the case for friends and family who knew of their AD.

Participant 12 discussed how she received negative comments from others about her condition, but this was mainly from the less-developed countries that she had visited to meet family. She described how people in these countries are more "direct" and have "less etiquette" than those in the UK.

DISCUSSION

Summary of Results

This study highlighted that many participants reported a poor body image and confidence. Indeed, the visibility of the condition appeared to affect participants greatly because they felt stigmatised. Participants offered explanations unique to their own life experiences as to why they might have developed AD. The findings also highlighted a possible lack of public awareness surrounding AD, as well as lack of empathy from family and friends. While many participants were keen for others to know more about the condition, many did not engage in speaking about the impact of their condition to friends or family as they did not want to be perceived in a negative light.

WHY DID PARTICIPANTS FEEL MISUNDERSTOOD BY THEIR HEALTH CARE PROFESSIONALS?

The qualitative methodology of the study elicited complexities in relationships between doctors and patients with AD not apparent in previous studies. Important among these was the appreciation by some participants that time considerations and other pressures may explain the apparent failings of practitioners. The finding that some patients felt that their doctor was a medical technician whose role was to physically treat their skin disease, and that the psychological implications were not within the doctor's remit, is consistent with the result of a New Zealand study that 37% of general practice patients with psychiatric symptoms had not disclosed them to their GP.[8] Cited reasons for not reporting psychiatric symptoms included a perception that a GP is not the most appropriate person to talk to, or that mental health issues should not be discussed, the stigma of mental illness, and factors related to healthcare system, such as time pressures in the consultation. Many participants did not view their HCP as a source of psychological support or management. An unexplored area is how stigmatisation of mental illness might be especially problematic in the setting of skin disease, which is already associated with considerable stigma. This may be accentuated by the perceived trivialisation of skin disease seen in this study and reported elsewhere.[9] Patients with AD may be even more reluctant to present psychological symptoms to their GP given these perceptions. This topic deserves further research.

WHY WERE BLACK AND MINORITY ETHNICITIES PARTICIPANTS LESS WILLING TO DISCLOSE THEIR CONDITION TO OTHERS?

In the authors' study, Black and minority ethnicities (BME) participants were less willing to talk about their condition, with one South-Asian participant acknowledging that her family in Pakistan were less accommodating of her condition than people in the UK. BME participants were also less willing to discuss the impact of AD on their personal relationships; however, this impact appeared to be greater in this subgroup in participants who did choose to discuss the subject. For example, Participant 2 discussed that she was forced to marry when she was 16 years old and, as a result of her husband and his family not being accepting of her AD, she had to resort to divorce. She blamed the failure of her marriage and inability to conceive purely on AD and the lack of understanding of the condition in her community. Skin diseases have special significance and are associated with various beliefs and taboos in different cultures.[10] In a multi-cultural society, such as that which exists in the UK, it is important for health professionals to acknowledge that some of their patients from ethnic minority groups may have additional or quite different psychological and social needs from those of the majority of the population. Myths and beliefs about skin diseases can have

a profound effect on the patient and affect their ability to cope. Understanding the implications of this is crucial to providing effective care for people with skin disease. Thompson et al.[11] reported in a study with South-Asian females born in Britain that vitiligo was related to stigmatisation and this was influenced by, and affected, cultural practices. Indeed, the majority of psychodermatology research has been conducted with White Western populations.[11]

STRENGTHS AND LIMITATIONS

This is among the first qualitative studies exploring QoL and mental health in adults with AD. Unlike most studies exploring QoL in adults with skin conditions, the authors' study had an ethnically diverse and large sample, which allowed for comparisons between subgroups because BME participants comprised almost one-half of the study sample. Issues such as the role of AD in intimate relationships and the implications of visibility in AD were among factors that the study was able to explore, but have not been explored widely in quantitative studies.[6] However, the authors' study lacked male participants, which does not allow for comparison between the sexes, and the findings may not reflect the experiences of males with AD. Additionally, AD diagnosis in the study was self-reported using demographic questionnaires; the questions did, however, explore details surrounding diagnosis, disease duration, and treatment for AD. Additionally, a large sample size of participants would have allowed for a more in-depth analysis and exploration of differences between participant groups.

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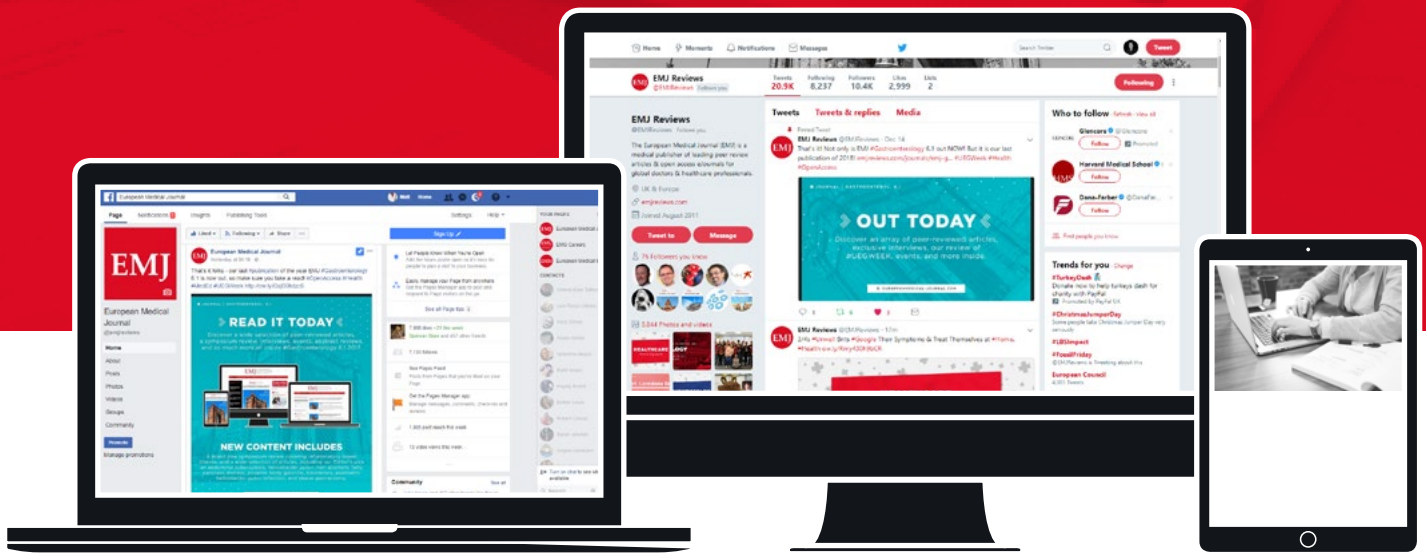

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Lupus Panniculitis in Association with Anti-Phospholipid Antibody Syndrome on a Background of Systemic Lupus Erythematosus: A Case Report and Literature Review

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Disclosure: The authors have declared no conflicts of interest.

Acknowledgements: Ethical approval was taken in this study from an institutional review board, and consent to participate was taken from the patient's guardian with informed verbal consent.

Received: 19.11.2019

Accepted: 22.01.2020

Keywords: Autoimmune, biopsy, discoid, lupus, panniculitis.

Citation: EMJ Allergy Immunol. 2020;10.33590/emjallergyimmunol/19-00195

Abstract

Lupus panniculitis occurs in 1–3% of the patients diagnosed with systemic lupus erythematosus (SLE) and 10% of the patients diagnosed with discoid lupus erythematosus (DLE). It is a disorder of autoimmune origin, manifesting as deep erythematous plaques and nodules involving the trunk, breasts, buttocks, face, and proximal extremities. It does not commonly ulcerate. This report highlights the case of a 22-year-old Asian female with a history of coeliac disease and significant family history of antiphospholipid antibody syndrome (APS) who presented with fever, malaise, weight loss, and subcutaneous non-tender nodules over the forearm, back, bilateral thighs, and feet. Laboratory investigations revealed positive antinuclear antibodies, anti-Ro/SSA antibody, and lupus anticoagulant, resulting in a diagnosis of APS. Biopsies of lesions were consistent with findings of lupus panniculitis. Every case of SLE and DLE with discrete skin lesions should be reviewed for any distinct entity such as lupus panniculitis, as it may be associated with greater risk of flares and systemic involvement. The purpose of this case report is to emphasise that early diagnosis and prompt treatment is crucial to improving the prognosis of such patients.

INTRODUCTION

Lupus panniculitis, also known as lupus profundus,[1] is characterised by chronic and recurrent inflammatory lesions of subcutaneous tissue.[2] It mostly occurs as a primary disorder but could also be associated with underlying systemic involvement in discoid lupus erythematosus

(DLE).[3] The terminology lupus panniculitis was first coined by Kaposi[4] in 1883. It usually occurs in the age range of 20–60 years old with a female predominance of 2:1.[2,5] It presents as a firm, fixed, hard skin lesion that may or may not be tender.[6] The diagnosis is usually performed by clinical correlation, histological evidence, immunofluorescence, and autoimmune profile.[6] Systemic lupus erythematosus (SLE) is an autoimmune disorder that could potentially involve any organ or system.[7] Cutaneous lupus erythematosus, usually a benign disease, can become complicated in 1–3% of patients and progress into lupus profundus.[8]

CASE PRESENTATION

A 22-year-old female of Asian descent with a past medical history of coeliac disease (CD) and positive family history of anti-phospholipid antibody syndrome (APS) in a second-degree relative presented with fever, generalised weakness, miscarriages in two previous pregnancies, and unintentional weight loss. She also presented with arthralgia, alopecia, photosensitivity, heavy menstrual blood flow, bluish discoloration of the fingers on exposure to cold, and recurrent oral ulcers. She developed non-tender subcutaneous nodules that formerly involved the forearm and later involved the back and bilateral thighs and feet. She denied facial rash, easy bruising, seizures, psychosis, proximal muscle weakness, cough, chest pain, diarrhoea, and blood in sputum. She was treated empirically with intravenous paracetamol (1 g every 8 hours) and corticosteroids (hydrocortisone 100 mg, every 8 hours).

The physical examination was unremarkable except for mild pallor; swelling in wrists, ankles, and small joints of the hands; periorbital puffiness; oral ulcers; non-scarring alopecia; and non-tender subcutaneous nodules over the forearm, back, and bilateral thighs (Figure 1). Laboratory workup showed haemoglobin: 10.2 g/dL with mean corpuscular volume: 70 fL; total leucocyte count: $9x10^3$ u/L; platelets: $30x10^3$ U/L; total bilirubin: 0.86 µmol/L with direct component of 0.23 µmol/L; alanine transaminase: 84 U/L, aspartate transaminase: 65 U/L, alkaline phosphatase: 140 IU/L; and gamma-glutamyl-transferase: 113 U/L. Other baseline investigations such as erythrocyte sedimentation rate and C-reactive protein were within normal limits. Based on suspected history, an autoimmune profile was sent which showed positivity for antinuclear antibodies (ANA) (2+, granular pattern), anti-dsDNA (40 U/mL), anti-Ro/SSA antibody (14 U/mL), and lupus anticoagulant antibody, whilst anti-La and other antibodies panel were negative, along with normal complement levels. The differential consideration at this point included SLE, mixed connective tissue disease, APS, Sjogren syndrome, rheumatic fever, and hypothyroidism. Based on blood workup, the initial diagnosis of SLE with APS was made and the patient was scheduled for skin-biopsy for the subcutaneous nodules.

Biopsy of the skin nodule showed lobular panniculitis, hyaline degeneration of fat, and lymphocytic infiltrate with scattered plasma cells, with no epidermal atrophy and no evidence of vasculitis (Figure 2). Immunofluorescence studies demonstrate deposits of IgM and complement 3 (C3) along the dermoepidermal junction, confirming the diagnosis of panniculitis in association with APS on a background of SLE. However, no specific feature suggestive of APS was present in the skin biopsy. The patient was managed initially with steroids (methylprednisolone 20 mg, twice daily), and hydroxychloroquine (HCQ) in a dose of 200 mg, every 12 hours. The general condition improved within a week; the patient was discharged on oral corticosteroids (1 mg/kg) and mycophenolate mofetil (500 mg, twice daily), and they were followed-up in the ambulatory setting within 2 weeks with a much-improved condition. Anticoagulant (warfarin 5 mg every 24 hours) was then given at the outpatient follow-up after 2 weeks. The patient was continued on the medications and was scheduled for monthly out-patient follow-up.

DISCUSSION

Lupus panniculitis is characterised by the development of painful indurated dermohypodermal nodules or plaques, typically affecting the thighs, the upper arms, or the cheek area of the face.[9] Bednarek et al.[10] reported in their study that in patients diagnosed with SLE, only 1–3% develop lupus panniculitis, while in patients diagnosed with DLE, this number can increase up to 10%.[2]

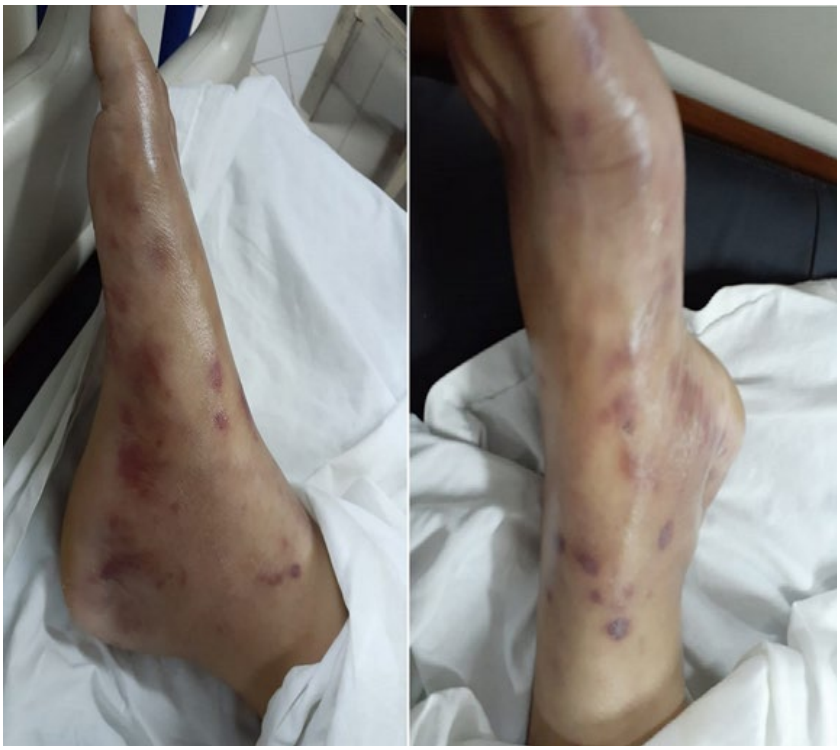

Figure 1: A patient presenting with non-tender subcutaneous nodules over the feet.

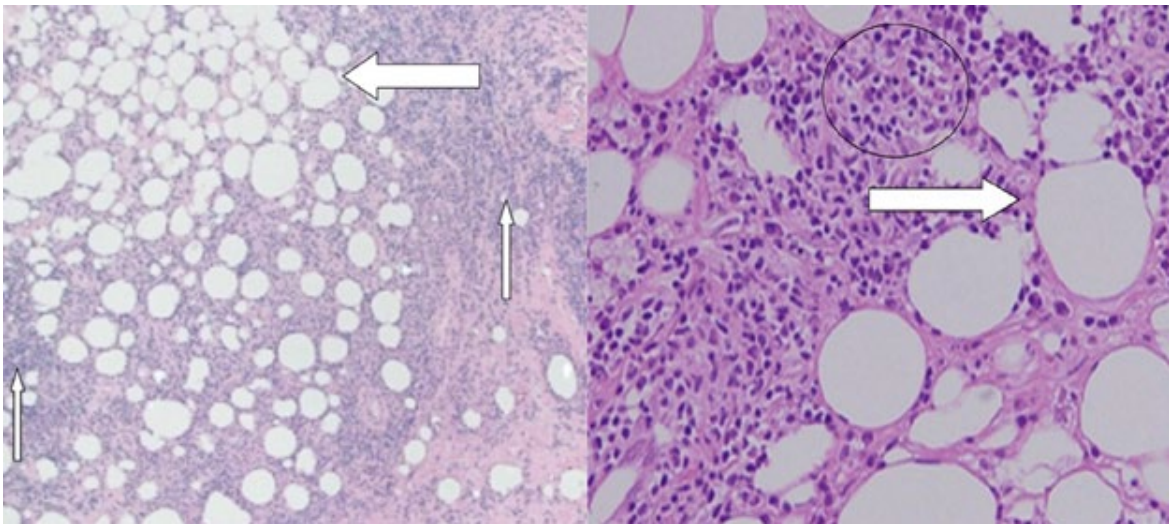

Figure 2: A) The hyaline degeneration of fat (thick arrow) with lymphocyte infiltration and plasma cells (thin arrows). B) The lobular panniculitis, fat degeneration (marked with an arrow), and inflammatory cells (marked with a circle).

The terminology 'lupus panniculitis' was first introduced by Kaposi[4] in 1883. The disease has a female to male ratio of 2:1, occurring predominantly in the age group of 20–60 years old.[5] The illness manifests itself as deep erythematous plaques and nodules, involving the trunk, breasts, buttocks, face, and proximal extremities. It does not commonly ulcerate. The lesions may or may not be tender, depending upon the severity, and often heals with scarring and atrophy which can lead to significant cosmetic disfigurement.[11] The presentation is mostly of firm, fixed, hard lesions, which have the propensity to involve the fatty tissue, ultimately leading to calcification or atrophy of the lesion.[12]

In patients with such a presentation, other inflammatory disorders such as factitial panniculitis, traumatic panniculitis, morphea profundus, dermatomyositis, and subcutaneous panniculitis-like T cell lymphoma should be considered and ruled out. Amongst these, the greatest mimic is cutaneous T cell lymphoma, though it does need to be kept in mind as it has an aggressive course and involves poor prognosis.[13] The diagnosis of lupus panniculitis involves clinical correlation, histological evidence, immunofluorescence, and autoimmune profile.[14] In approximately 50% of cases a biopsy of the specimen leads to the diagnosis, revealing the typical changes such as perivascular and peri-appendageal lymphocytic inflammation, hydropic degeneration of basal layer, hyperkeratosis, thickened basement membrane, interface changes, epidermal atrophy, and hyaline sclerosis of lobules.[15] Immunofluorescence studies are also an important subset helping in the diagnosis; they display the linear deposits of IgM and C3 along the dermoepidermal junction. If the biopsy gives equivocal results, the lupus band test is often performed. However, the ultimate diagnosis requires the clinical background with these pathological features and positive ANA occurs in about 50–85% of patients.[14] In patients who test ANA negative, the diagnosis should solely rely on histopathological evidence.[15] Lupus pannulitis has been rarely reported with APS, and usually without any systemic involvements.[16] Also of note, eyelid oedema is the most common ocular involvement reported with lupus panniculitis.[17]

The 22-year-old Asian female, a known case of CD with a significant family history of APS, presented with fever, malaise, and weight loss. Her medical history was significant for oral ulcers, alopecia, Raynaud's phenomenon, and recurrent miscarriages. She had subcutaneous non-tender nodules located on the arms, thigh, and buttock region. Laboratory investigations revealed positive ANA, anti-Ro/SSA antibody, and lupus anticoagulant, resulting in a diagnosis of APS on a background of SLE. Biopsies of lesions were consistent with findings of lupus panniculitis, ultimately leading to a diagnosis of lupus panniculitis in association with APS, on the background of SLE. The patient was given steroids (methylprednisolone, 1 mg/kg) along with mycophenolate mofetil (500 mg twice daily) and was followed-up in the ambulatory setting within 2 weeks. Anticoagulant (warfarin, 5 mg daily) was added to the patient prescription at the outpatient follow-up after 2 weeks.

The treatment of lupus panniculitis is challenging because there are no specific indications or medication recommendations in the guidelines.[18] Antimalarial drugs are believed to bring improvement in mild cases of isolated lupus panniculitis.[19] Chloroquine in a dose of 200–250 mg a day and HCQ in a dose of 200–400 mg a day is typically recommended. Usually, an eye examination is carried out during HCQ therapy in the first year if forced by a higher ophthalmolotoxic profile, but the risk remains small in therapeutic doses. HCQ is being used in SLE patients with mild disease and is known to decrease the need for steroids.[18]

When lupus panniculitis co-occurs with SLE, a combination of antimalarial and steroids is prescribed. Systemic steroids are reserved for aggressive and resistant cases.[11] In association with APS, lifelong anticoagulant therapy is usually added to the empiric treatment to prevent the recurrence of thromboembolism.[20] Surgical intervention is indicated when all other possible approaches have failed to treat lupus panniculitis.[20]

CONCLUSION

Every case of SLE and discoid lupus with discrete skin lesions should be reviewed for any distinct entity such as lupus panniculitis, as it may be associated with greater risk of flares and systemic involvement. The purpose of this case report was to emphasise that early diagnosis and prompt treatment is crucial to improving the prognosis of patients with lupus panniculitis. It is considered the least common variety of cutaneous manifestations of lupus erythematosus, but it can be considered an initial presenting manifestation of SLE.

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Post Fever Uveoretinal Manifestations in an Immunocompetent Individual

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Received: 10.04.20

Accepted: 18.05.20

Keywords: Choroiditis, chikungunya, dengue, macular oedema, maculopathy, multifocal retinitis, neuroretinitis, retinitis, rickettsiosis, typhoid, West Nile.

Citation: EMJ Allergy Immunol. 2020;5[1]:91-105.

Abstract

Background: Post fever uveoretinal sequelae (PFURS) are the various uveoretinal manifestations seen after a systemic febrile illness in an immunocompetent individual caused by bacteria, viruses, and protozoa. These may be the result of a direct invasion by the pathogen or by indirect mechanism mediated through immune mechanisms.

Method: The authors aim to review the ocular manifestations, utility of relevant diagnostic tests, management, and prognosis of PFURS. A comprehensive literature search was conducted on PubMed and Google Scholar databases with the search words "retinitis", "choroiditis", "neuroretinitis", "macular edema", "maculopathy", "multifocal retinitis", "chikungunya", "dengue", "West Nile", "typhoid", and "rickettsiosis". Only articles published or translated into English language were considered. The key data were extracted, evaluated, and combined.

Results: The authors search yielded 95 articles for the period between 1986 and May 2020. Painless blurring of vision was the most common symptom. Patients can have varied posterior segment manifestations, including vitritis, focal and multifocal patches of retinitis which could be unilateral or bilateral, optic nerve involvement, serous detachment at the macula, macular oedema, and localised involvement of the retinal vessels in the form of beading of the vessel wall, tortuosity, and perivascular sheathing.

Conclusion: PFURS presents with a similar morphological pattern irrespective of the aetiology and follows a preset natural course before resolution. Treatment may or may not be required. Treating physicians need to be aware of this important ophthalmic condition even after complete resolution of fever.

INTRODUCTION

Post fever uveoretinal sequelae (PFURS) is used for describing the various uveoretinal manifestations seen 2–4 weeks after a systemic febrile illness in an immunocompetent individual with positive serology for bacteria, viruses, or protozoa. These manifestations may be the result of a direct invasion by the pathogen or by indirect mechanism mediated

through immune mechanisms.[1] Ocular symptoms include sudden, painless diminution of vision, black dots, flashes of light, loss of one-half of visual field, and central black outs. Patients can have varied uveoretinal manifestations including solitary and multifocal patches of retinitis, serous detachment at the macula, macular oedema, and localised/generalised involvement of the retinal vessels in the form of beading of the vessel wall, tortuosity, and perivascular sheathing and optic nerve involvement.[1,2] Irrespective of the cause of the fever, clinical presentations of cases are similar with predominant signs at the posterior pole of the retina and a favourable response to steroids may suggest a possible immunological basis for this condition.[1-7]

Epidemic retinitis (ER) is a retinitis post-febrile illness commonly caused by *Rickettsia*, dengue, chikungunya, West Nile virus (WNV), and several other as yet unknown organisms, generally seen in tropical countries.[2,8,9] ER has been previously described by different authors as "post-fever retinitis" or "acute multifocal retinitis."[10,11] Herein, various pathogens implicated in PFURS are discussed. Table 1 summarises various studies in medical literature.[4,5,12-30]

VIRAL

Chikungunya, dengue, and Zika viruses have emerged as increasingly important arboviruses that cause ophthalmic manifestations. The global expansion of these arboviruses was preceded by the global spread of their vectors. These arboviruses have common and very similar symptoms such as fever, skin rashes, malaise, headache, neutropenia, and lymphopenia.[31]

Dengue

Dengue maculopathy is a common posterior segment condition and its incidence may correlate with the severity of systemic disease.[12] Common ophthalmic manifestations include subconjunctival, vitreous, and retinal haemorrhages; anterior and posterior uveitis; optic neuritis; and maculopathies such as foveolitis, haemorrhage, and oedema. Main symptoms include blurring of vision, scotomata, metamorphopsia, and floaters.[12]

Symptoms of dengue maculopathy start at a mean of 6.9 days after the onset of fever. Poorer visual acuity may be seen in patients with macular oedema or foveolitis, and this correlates with the severity of macular oedema. There may be presence of well-defined, yellowish subretinal lesions in the macula along with retinal striae radiating around the fovea (foveolitis). These lesions may represent disruption of photoreceptors, the outer neurosensory retina, and the inner segment/outer segment (IS/OS) junction, along with dot and blot and macular haemorrhages which corresponds to areas of scotomata.[32-36]

The presence of foveolitis in patients with maculopathy was 7%. In the study by Pang and Loh,[37] four out of six patients had bilateral disease. Some eyes had concurrent findings of superior temporal branch vein occlusion and macular oedema, while some had associated foveolitis and vasculitis suggestive of an inflammatory pathophysiology. Haemorrhagic retinopathy associated with dengue haemorrhagic fever is related to the induced thrombocytopenia. The onset of visual symptoms is usually observed within 1 day from the resolution of fever and at the nadir of the thrombocytopenia.[37] Secondary dengue infection may manifest as retinitis with signs of microvascular occlusions in the retina.[13]

Changes such as anterior uveitis, exudative maculopathy, choroidal effusion, Roth spots, vasculitis, exudative retinal detachment, and panophthalmitis are rare.[1] Mean complement C3 levels were lower in subjects with dengue maculopathy than in those without. The appearance of maculopathy 1 week after onset of fever suggests that dengue maculopathy is the result of an immune-mediated process and not a direct consequence of viral invasion of ocular tissue.[12] Acute macular neuroretinopathy (AMN) has been recently reported to be an unusual manifestation of dengue maculopathy.[38,39] AMN presents with hyper-reflectivity of the outer retina (outer plexiform layer and outer nuclear layer), and disruption of ellipsoid zone, external limiting membrane, and interdigitation zone.[39]

Fundus fluorescein angiography is a useful imaging modality to determine the extent and severity of retinal manifestations such as maculopathy and retinal vasculitis. Foveolitis appears as retinal pigment epithelial hyperfluorescence that appears in the early phase and persists till the late phase.

Table 1: Summary of the case report/series published in the medical literature.

Paper	Design	Number of cases	Age/ sex	Interval between fever and ocular symptom	Infection	Ocular symptoms	Ocular signs	Investigations	Treatment	Follow-up	Outcome
Lalitha et al.,[4] 2007	Case series	37	M:F 21:16	33 days	Chikungunya	Photophobia, retrobulbar orbital pain, and conjunctivitis.	Granulomatous and nongranulomatous anterior uveitis, optic neuritis retrobulbar neuritis, dendritic lesions, and retinitis.	Single positive IgM chikungunya serologic test by ELISA.	Topical and systemic steroids	3 months	VA improved in 11 patients, remained same in 12, and worsened in 3.
Relhan et al.,[5] 2014	Case report		27-year-old M	6 weeks	Typhoid fever	Decreased vision 4 weeks after the onset of treatment, BCVA 20/125 N36 RE and 20/20 N6 LE. Grade 1 RAPD in the RE. Defective colour vision in the RE.	RE clear media with slight disc pallor with area of vasculitis superior to disc associated with multiple whitish fluffy areas of deep retinitis and a large NSD in the macular area. LE clear media, normal disc and foveal reflex, one discrete CWS superior to the disc, and a nasal area of retinal venous sheathing.	RE highly reflective and disorganised inner retinal layer with back scattering and underlying serous retinal detachment on OCT. Negative for HIV, tuberculosis, syphilis, connective tissue disorders, SLE, and rheumatoid arthritis.	Prednisolone (1 mg/kg body weight/day). Steroids were tapered over 2 months with regular monitoring.	6 months	BE: Complete resolution of all retinal lesions with pigmentary changes. Mild disc pallor in the RE. OCT at 6 months showed residual thinning of inner retinal layers over the lesion along with complete resolution of subfoveal NSD in the macula.
Su et al.,[12] 2007	Case series	197	M:F 119:78	7 days	Dengue fever	From mild BOV to catastrophic and severe blindness.	Retinal or choroidal vasculopathy with macular swelling, small white or yellow dots usually on the papillomacular bundle or close to the fovea, and intraretinal haemorrhages at the macula.	Blood samples: to evaluate complement C3 and C4 levels. Urine samples: quantification of urinary microalbumin by immunoturbidimetric method. FFA: mild arteriolar and/or venular leakage.	Supportive therapy	1 month	27 had dengue maculopathy and 15 had significant morbidity with severe visual impairment.
Koundanya et al.,[13] 2019	Case report		42-year-old F	7 years	Dengue fever	BOV in the RE for 5 days (VA 6/24 N18 RE and 6/6 N6 LE).	Dilated and tortuous superotemporal vein with multiple intraretinal haemorrhages and a patch of retinitis measuring approximately 2-disc diameter along the superotemporal arcade along with a serous detachment of the macula.	FFA of RE: areas of blocked fluorescence corresponding to the retinal haemorrhages and early hypofluoresence with late hyperfluorescence along the superotemporal arcade in right eye. OCT of RE: showed subfoveal fluid and hyperreflectivity of the inner retinal layers with loss of architecture over the patch of retinitis. NS-1 antigen test for dengue virus was positive. Serology for dengue IgG was positive but was negative for chikungunya, West Nile virus, and yellow fever. Dengue IgG: IgM ratio was 1.8, suggestive of secondary dengue infection.	Oral corticosteroids (1 mg/kg)	2 months	VA in RE improved to 6/6 N6. Resolving retinal haemorrhages and retinitis patch. OCT of the RE showed a decrease in the thickness of the inner retinal layers and resolving oedema.

Table 1 continued.

Paper	Design	Number of cases	Age/ sex	Interval between fever and ocular symptom	Infection	Ocular symptoms	Ocular signs	Investigations	Treatment	Follow-up	Outcome
Mahendradas et al.,[14] 2008	Case series	9	M:F 5:4	4–12 weeks (median: 6 weeks)	Chikungunya	BOV	Vitritis and a hyperaemic disc with an area of confluent retinal opacity suggestive of retinitis in the posterior pole with surrounding retinal and macular oedema.	FFA: early hypofluorescence and late hyperfluorescence with disc leakage. OCT: increased reflectivity in the NFL zone corresponding to the areas of retinitis with after shadowing. Fluid-filled spaces in the outer retina with subfoveal serous detachment Serum: chikungunya IgM antibody. Serological tests for HSV (IgG and IgM), CMV (IgM), dengue IgM, and ELISA for HIV I and II were negative.	Systemic acyclovir; prednisolone (40 mg/day orally for 1 week), which was then tapered over a period of 6 weeks along with topical 0.1% diclofenac sodium four times a day.	6 weeks	VA improved with resolving retinitis.
Mahesh et al.,[15] 2009	Case report		48-year-old F	2 weeks	Chikungunya	BOV, VA 20/80 N18 RE, 20/60 N6 LE.	Few vitreous cells, optic disc oedema, intraretinal haemorrhages, peripapillary CWS, and areas of retinitis with macular star in BE.	ESR: 61 mm in 1 hour (Westergren's method). Haemoglobin: 12.5 gm%. Total count: 14,000 cells/mm^3 Differential count showed polymorphs 62%, lymphocytes 28%, eosinophils 8%, and basophils 2%. Platelet count: 1.8 lakhs/mm^3. Random blood sugar: 240 mg%. Blood urea: 30 mg%; serum creatinine: 0.8 mg/dL. SGOT: 42 U/L; SGPT: 67 U/L. ELISA test for HIV and VDRL test were negative. Chikungunya (Card) IgM ELISA test was positive. PCR test: confirmed the presence of chikungunya virus infection. FFA: leakage from disc margins and from peripapillary vessels and blocked fluorescence due to retinal haemorrhage.	Tablet Prednisolone 1 mg/kg body weight was started and tapered over 6 weeks.		BCVA improved to 20/30, N6 in RE and 20/20, N6 in the LE. Bilateral resolution of disc oedema with decrease in the retinal haemorrhages and CWS.
Prabhushankar et al.,[16] 2017	Case report		59-year-old M	28 days	Typhoid fever	Diminution of vision in RE (VA 2/60 RE, 20/20 LE).	RE: showed white fluffy lesions along the superior and inferior arcades with superficial haemorrhages in around the macula with a macular star suggestive of retinitis. LE: fundus showed few dispersed retinitis lesions with superficial haemorrhage along the superior arcade with intact foveal reflex.	OCT: RE underlying macular serous retinal detachment was noted. Blood tests were done to rule out VDRL and HIV status. X-cyton analysis of the AC aspirate was negative for organisms including *Mycobacterial tuberculosis*, *Toxoplasma gondii*, HSV, CMV, and VZV.	Oral prednisolone 1 mg/kg body weight which was tapered over 2 months.	3 months	Improvement in the BCVA in RE to 6/6 which was maintained on further visits. Fundus examination revealed resolving lesions in BE and OCT of the RE showed resolution of the serous detachment.

Table 1 continued.

Paper	Design	Number of cases	Age/ sex	Interval between fever and ocular symptom	Infection	Ocular symptoms	Ocular signs	Investigations	Treatment	Follow-up	Outcome
Fusco et al.,[17]	Case report		23-year-old M	20 days	*Salmonella typhi*	BOV BE, VA 20/40 RE, 20/200 LE.	Blurred disc margins especially in the nasal half, arterial narrowing, venous dilatation with increased tortuosity, exudates of varying size and flame haemorrhages localised at the posterior pole and in the midretinal periphery.	VF: sector scotoma involving blind spot. Colour vision: yellow blue defect. CBC: leukopenia. ESR: raised. Widal's test: positive at significant titres. Stool culture: grew *S. typhi*.	Patient was allergic to chloramphenicol so he was treated with 2 g ampicillin 6 hourly for 4 weeks and locally long-acting corticosteroids retro bulbar injection.	3 months	Haemorrhages and exudates significantly diminished. Some gain in VA.
Murthy et al.[18] 2008	Case report		35/M	21 days	Chikungunya	BOV RE (VA CF 2 m RE, 20/20 LE)	RE: areas of retinitis and haemorrhages in the posterior pole and hyperaemia and blurring of the disc margins (neuroretinitis). LE: a patch of retinitis was seen nasal to the optic disc.	FFA: areas of capillary nonperfusion corresponding to the retinitis lesions. OCT: areas of retinal destruction. ESR: 38 mm/hour. Haematological and rheological parameters, coagulation profile, blood sugar, liver and renal function, urine analysis, and chest X-ray were normal. VDRL test for syphilis and Mantoux test were negative. ELISA: IgM and IgG positivity for HSV, and only IgG positivity for CMV and VZV. ELISA: HIV and toxoplasma were negative. Aqueous: positive for HSV.	Intravenous acyclovir 1,500 mg/m^2/day. Oral steroids 1 mg/kg body weight. Oral acyclovir and intravitreal ganciclovir 2 mg in 0.05 mL in BE.	5 months	Retinal lesions had healed well and his BCVA was 20/120 and 20/20 in the RE and LE, respectively.
Siqueira et al.[19] 2004	Case report		1/M	13 days	Dengue fever	BOV BE; VA: RE 6/30 LE 6/60.	No AC or vitreous cells BE; preretinal haemorrhages at equator; CWS at macula; and peripheral vascular sheathing BE.	FFA: areas of CNP in both the equator and macula. MRI brain and carotid Doppler studies: normal.	Oral anti-platelet therapy; LE Pars plana vitrectomy; RE PRP.	2 years	Poor VA in LE; no further retinal vasculitis.

Table 1 continued.

Paper	Design	Number of cases	Age/ sex	Interval between fever and ocular symptom	Infection	Ocular symptoms	Ocular signs	Investigations	Treatment	Follow-up	Outcome
Lim et al.[20] 2004	Case series	6	M:F 1:5	6.8 days	Dengue fever	BOV (90.9%); VA range from 6/6 to HM; scotomas (36.4%).	AC cells (18.2%); vitreous cells (18.2%); RPE changes (27.3%); RPE discoloration (9.1%); retinal haemorrhage (36.4%); retinal vasculitis (9.1%); intraretinal white lesions (18.2%); macular oedema (54.5%).	FFA: arteriolar focal knobby hyperfluorescence in the macula with mild vascular wall staining and leakage (27.3%); early hyperfluorescent spots at the level of the RPE (36.4%); and transmission defects (36.4%). ICG: Diffuse choroidal hyperfluorescence (81.8%). HVF and Amsler chart: central scotoma (9.1%).	No treatment (1 case); steroid therapy (1 topical, 2 periocular, 2 oral).	2 weeks to 4 months	RPE discoloration over affected areas; partial recovery of VA (3 cases); VA stable (3 cases).
Sanjay et al.[21] 2008	Case Series				Dengue fever	Diminution of vision from 6/6 to CF, impaired colour vision, scotomas, enlarged blind spot.	Retinal oedema, retinal haemorrhages, CWS, optic disc swelling, and optic disc atrophy.	mfERG: centrocecal scotoma. pVEP: delayed P100 latency and absent response. MRI: oedema of optic nerve sheath complex. HVF: central scotoma, paracentral scotoma, enlarged blind spot.		6 months to 1 year	6/9 with impaired colour vision and paracentral scotoma (1 eye). No PL RE and resolved VF defects in LE (1 case). 6/6 with signs and symptoms completely reduced (1 case).
Shanmugan et al.,[22] 2019	Case report		17/M	2 weeks	*Rickettsia*	Diminished vision in BE for 10 days, 6/36 RE, and 1/60 LE.	RE soft exudates and haemorrhage suggestive of retinitis. LE retinal whitening and retinal haemorrhages.	RE OCT: vitreous cells and NSD at fovea. OCTA: distortion of the FAZ with CNP areas in SCP and DCP. Choriocapillary layer in the RE: signal void areas corresponding to soft exudates. LE OCT: vitreous cells and NSD at fovea SCP and DCP showed multiple CNP areas, pruning of vessels temporal to the disc, and signal void areas. Choriocapillary slab in the LE: absence of signals at areas corresponding to soft exudates. Positive for OX-2 antigen and negative for OX-K and OX-19.	Oral doxycycline and oral prednisolone.	6 months	BCVA was 6/9 RE and 6/12 LE. Complete resolution of soft exudates and haemorrhages was noted in BE. RE: SCP and DCP showed enlarged FAZ, reduction in the CNP area, and reorganisation of the capillary network. LE: SCP showed reorganisation of capillary network at macula with decrease in CNP area and disappearance of abnormal vessels temporal to the disc. LE: DCP showed decrease in CNP area with minimal distortion of FAZ.
Haritoglou et al.,[23] 2002	Case report		1/F	1 day	Dengue fever	BOV BE; VA 6/150 BE; colour vision severely affected.	Small haemorrhages at NFL; exudative maculopathy BE.	Electrophysiological exam: prolonged latencies, reduced amplitude of visually evoked cortical responses, mild reduction of amplitudes in mfERG BE. Arden colour contrast test: abnormal.	No treatment.	8 weeks	VA improved: RE 6/30 LE 6/9.5.

Table 1 continued.

Paper	Design	Number of cases	Age/ sex	Interval between fever and ocular symptom	Infection	Ocular symptoms	Ocular signs	Investigations	Treatment	Follow-up	Outcome
Yamamoto et al.,[24] 2002	Case report		1/M	24 days	Dengue fever	BOV BE; VA CF BE.	Fundoscopy was normal; optic neuropathy suspected as the cause of visual disturbance.	MRI brain: no abnormalities in the optic nerves, cerebellum, or cerebrum. MRI spine: multiple high-intensity spotty lesions from Th-7 to Th-11. Lumbar puncture: mild elevation of protein and pleocytosis.	IVMP.	NA	Mild visual disturbance BE.
Cruz-Villegas et al.,[25] 2003	Case report		1/M	3 days	Dengue fever	BOV BE; VA: RE 6/24 LE 6/120; scotomas BE; ocular pain BE.	AC cells BE; AC shallow BE; extensive bilateral choroidal effusions.	CT brain and MRI brain: normal. Lumbar puncture: negative.	Topical prednisolone.	1 week	VA 6/6 BE; AC deeper with trace of cells; choroidal effusions subsided.
Nainiwal et al.,[26] 2005	Case report		1/F	2 days	Dengue fever	BOV BE; VA: RE PL LE 6/18.	Vitreous haemorrhage BE.		Standard supportive care (4 cases); platelet transfusion (2 cases).		
Chlebicki et al.,[27] 2005	Case series	4	M:F 1:3	625 days	Dengue fever	BOV (100%); VA reduced (100%); metamorphopsia (25%).	Blot haemorrhages within the vascular arcades BE (100%).		Standard supportive care (4 cases); platelet transfusion (2 cases).		Complete resolution within 2 days (3 cases); reduced VA and metamorphopsia after 2 months.
Mehta,[28] 2005	Case series	5	M:F 4:1		Dengue fever	VA 6/6 (20%); rest had no VA performed.	SCH (60%); Roth spots (10%); intraretinal haemorrhage (60%); and yellow thickening in choroid and retina (40%).				
Preechawat et al.,[29] 2005	Case report		1/M	10 days	Dengue fever	BOV BE; VA CF BE.	Flame-shaped haemorrhage at fovea RE; mild bilateral optic disc hyperaemia.	FFA: no disc leakage. HVF: bilateral cecocentral scotomas. Lumbar puncture and brain and orbit MRI: normal.	IVMP followed by OPNL.		VA: 6/6 BE; colour vision: normal.
Menia et al.,[30] 2019	Case report		43/M	5 days	Influenza Type A	BOV LE; VA 3/60 LE.	Yellowish-white, coin-shaped lesion at the fovea.	SD-OCT: hyperreflective lesion at fovea involving all retinal layers. H1N1: positive. HIV: negative.	Oral corticosteroids.	2 months	Lesion healed at 2 months.

Table 1: Shows the published literature on post fever uveoretinal sequelae.

AC: anterior chamber; BCVA: best corrected visual acuity; BOV: blurring of vision; BE: both eyes; CMV: cytomegalovirus; CNP: capillary nonperfusion; CBC; complete blood count; CF: counting fingers; CWS: cotton-wool spots; DCP: deep capillary plexus; ESR: erythrocyte sedimentation rate; F: female; FAZ: foveal avascular zone; FFA: Fundus fluorescein angiography; HM: hand motion; HSV: herpes simplex virus; HVF: Humphrey's visual field test; ICG: indocyanine green angiography; IVMP: intravenous methylprednisolone; LE: left eye; M: male; mfERG: multifocal electroretinogram; NA: not available; NFL: nerve fibre layer; NSD: neurosensory detachment; OCT: optical coherence tomography; OCTA: optical coherence tomography angiography; OPNL: outer plexiform and nuclear layer; PRP: panretinal photocoagulation; pVEP: pattern visual evoked potential; PL: perception of light; RAPD: relative afferent pupillary defect; RE: right eye; RPE: retinal pigment epithelium; SD-OCT: spectral domain optical coherence tomography; SCH: subconjunctival haemorrhage; SCP: superficial capillary plexus; SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum pyruvic acid transaminase; SLE: systemic lupus erythematosus; VDRL: venereal diseases research laboratory test; VA: visual acuity; VF: visual field; VZV: varicella zoster virus.

There may be presence of macular periphlebitis and occlusion. Common findings include disc leakage, arteriolar leakage, and macular oedema. Indocyanine green angiography may show presence of hypocyanescent spots suggestive of the involvement of choriocapillaris and the retinal pigment epithelium.[39-41]

Chikungunya Virus

Chikungunya fever is a common arthropod-borne viral illness that commonly affects Asian countries and Pacific islands. Epidemics of chikungunya have recently been reported from several Asian countries, such as India.[2,42-44] Ophthalmic manifestations may be unilateral or bilateral. Retinitis presents between 2 and 4 weeks after febrile period of systemic disease.[33] Chikungunya retinitis can be differentiated from herpetic retinitis by less vitreous reaction and confluent posterior pole retinitis, whereas acute retinal necrosis is characterised by intense vitritis and peripheral multifocal or disseminated retinitis.[45,46] It can also simulate WNV retinitis, therefore, it is important to assess systemic symptoms to differentiate the aetiology of the manifestation.[47] All these patients have a good visual outcome with almost total recovery within 10–12 weeks.[9]

It is presumed that an immune dysregulation, superantigen induction, hypersensitivity reaction, and molecular mimicry between stimulating virus-derived antigens and normal or altered host tissue proteins may be the cause of the optic nerve damage, while some hypothesise that ocular manifestations associated with chikungunya fever may be an immune-mediated process-like production of autoantibody rather than a direct viral infection.[4]

The authors' experience shows that anterior uveitis and retinitis are the most common ocular manifestations associated with chikungunya, with a typically benign clinical course.[14] However, long-term sequelae of the retinitis revealed thinning of the inner retinal layers.

Bilateral neuroretinitis associated with chikungunya infection has been reported.[15] Other viral infections caused by measles, influenza, Epstein–Barr, dengue, and Rift valley fever viruses can also present with neuroretinitis occurring subsequent to an acute viral systemic illness. Vishwanath et al.[1] showed that a patient who was positive for IgM chikungunya virus had bilateral anterior nongranulomatous uveitis and retinitis with optic nerve involvement in one eye showed a favourable response to oral steroids.

Zika Virus

Zika virus ocular manifestations are usually mild, such as nonpurulent conjunctivitis in adults, though it may be linked to uveitis, maculopathy, and hypertensive iridocyclitis later.[48] Miranda et al.[49] described ocular findings in three patients with microcephaly and a presumed Zika virus infection. All six eyes had pigmentary maculopathy ranging from mild to pronounced. Some showed well-delineated macular chorioretinal atrophy with a hyperpigmented ring, while others had vascular tortuosity and pronounced early termination of the retinal vasculature, washed-out peripheral retina with a hypolucent spot, and scattered subretinal haemorrhages external to the macula on photographic evaluation. One characteristic finding seen was peripheral pigmentary changes and clustered atrophic lesions resembling grouped congenital albinotic spots (polar bear tracks).[49]

Some other studies have shown macular changes (thick pigment spots and/or chorioretinal atrophy) and optic nerve abnormalities (double ring hypoplasia, pallor, and/or increased cup-disc ratio).[50] Another case report described a patient with strongly positive value on a serum plaque reduction neutralisation technique with macular retinal pigment epithelium changes with a grey annulus around the fovea on posterior segment examination and disruption of outer retinal and retinal pigment epithelium integrity in the central macula evidenced on optical coherence tomography.[51]

The first signs of congenital ocular involvement related to Zika virus were reported in January 2016 in three Brazilian children with microcephaly who were born to a mother who had been infected with the virus during pregnancy.[50,52,53] The presence of these complications was substantiated by Freitas et al.[54] who identified that among 29 newborns with microcephaly, 10 children had ocular abnormalities. The lesions consisted of zones of chorioretinal pigmentation or atrophy and bilateral in 70% of cases. Optic nerve changes described were hypoplasia, disc pallor, or large cups.[54] These abnormalities

were increasingly frequent with smaller cranial circumference and if the symptoms of Zika virus infection occurred during the first trimester of pregnancy.[55] Also reported were atrophic and pigmented lesions resembling torpedo maculopathy, abnormal retinal vascular patterns, retinal haemorrhages, and lesions of the iris (coloboma) or lens (subluxation).[54-56]

Ebola Virus

Shantha et al.[57] have summarised a number of reports about the ophthalmic sequelae of Ebola virus disease in the recent and past outbreaks. The prevalence of uveitis has ranged from 18% to 34% of survivors; in their own series (from the recent outbreak in West Africa), more than one-third of those with uveitis were blind. In addition to cases of posterior uveitis, which can result in the retinal lesions described by Steptoe et al.,[58,59] there were cases of isolated anterior uveitis and intermediate uveitis. Other ophthalmic conditions included optic neuropathy and other neuro-ophthalmic problems in some,[60,61] while others progressed to phthisis.

As many as 20% of convalescent patients, who may be asymptomatic for up to 2 months, develop hypertensive uveitis characterised by ocular pain, photophobia, hyperlacrimation, foreign body sensation, red eye, and progressive visual loss.[62]

Ebola retinal lesions varied in size and shape, but distinctive linear borders with sharp angulations were characteristic. Multimodal imaging features varied according to severity and extent of retinal structures involved. Lesions appeared light grey on fundus photography and were predominantly nonpigmented.[58]

Influenza A (H1N1) Virus

Studies show nonconfluent cotton wool spots in H1N1 representing milder versions of ischaemic retinopathy. Visual acuity normalised over several months in some, whereas patients with bilateral peripapillary cotton wool spots took over 3 weeks to resolve.[63,64]

Ashfaq et al.[65] reported a case series of acute macular neuroretinopathy associated with virologically confirmed acute influenza virus Infection. Ocular symptoms range from pain, redness, and decreased visual acuity to uveal effusion syndrome and orbital inflammatory syndrome. Vision loss may also be caused by simultaneous retinal and lateral geniculate body infarction.[66]

West Nile Virus

Posterior segment manifestation of WNV include chorioretinitis or only retinitis, anterior uveitis, retinal occlusive vasculitis in which arterial involvement is greater than venous involvement, optic neuritis, and congenital chorioretinal scarring optic neuropathies.[67,68] The characteristic feature of WNV chorioretinitis is a curvilinear clustering of whitish-yellow chorioretinal scars with a 'target-like' appearance, following the course of the retinal nerve fibres.[69] Sivakumar et al.[3] reported a case series of WNV retinitis from South India which did not follow the classical pattern of WNV infection. Fundus examination revealed discrete, superficial, white retinitis; arteritis; phlebitis; and retinal haemorrhages with or without macular star. The fundus fluorescein angiography revealed areas of retinal inflammation with indistinct borders, vascular and optic disc leakage, vessel wall staining, or capillary nonperfusion.

Coronavirus

The most recent entrant to this list is the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) which was first detected in December 2019 in Wuhan, China.[70] This outbreak was suspected when numerous unexplained pneumonia cases occurred. It has been established that infectious droplets and body fluids can easily contaminate the human conjunctival epithelium. Respiratory viruses are capable of inducing ocular complications in infected patients, which then leads to respiratory infection. SARS-CoV-2 coronavirus disease-2019 (COVID-19) is predominantly transmitted through direct or indirect contact with mucous membranes in the eyes, mouth, or nose. The fact that exposed mucous membranes and unprotected eyes increased the risk of COVID-19 transmission suggests that exposure of unprotected eyes to SARS-CoV-2 could cause acute respiratory infection. Posterior segment manifestations were recently reported by Marinho et al.[71] They found hyper-reflective lesions at the level of ganglion cell and inner plexiform layers more prominently at the papillomacular bundle in both eyes and subtle cotton wool spots and microhaemorrhages along the retinal arcade.

BACTERIAL

Typhoid

In addition to causing enteric fever, septicaemia, gastroenteritis, and vasculitis, *Salmonella typhi* can affect the eye either by direct infection or rarely by immune-mediated mechanisms. Duke-Elder and Perkins[72] reported typhoid-related uveal complications including iritis, retinal haemorrhage, choroiditis endophthalmitis, panophthalmitis, vasculitis, and retinitis with macular neurosensory detachment post-typhoid fever.

Salmonella spp., including *enteritidis*, *typhimurium*, and *choleraesuis*, have been isolated from aqueous and vitreous samples in patients with endogenous endophthalmitis.[73]

Other posterior segment manifestations reported are frosted branch angiitis; bilateral chorioretinitis with stellate maculopathy; vitritis; multifocal patches of retinitis; macular oedema; disc involvement in the form of hyperaemia, oedema or sphincter haemorrhages; and localised retinal vascular sheathing.[74] Endogenous endophthalmitis is a rare complication of salmonella infections occurring in immunocompromised patients.[75] Patients with bilateral confluent retinitis had significantly high Widal titres.[76] Bilateral retinitis following typhoid fever was also reported.[16,77] Multifocal choroiditis following simultaneous hepatitis A, typhoid fever, and yellow fever vaccination is an inflammatory disease characterised by multiple, small, yellow fundus lesions and vitreous inflammation which is because of the involvement of the eye which may be a result of direct invasion or immune-mediated phenomenon.[75]

Rickettsioses

The spotted fever group includes Mediterranean spotted fever (MSF), Rocky Mountain spotted fever, and numerous other rickettsioses. MSF, also called 'boutonneuse' fever or tick-borne rickettsiosis, is caused by the organism *Rickettsia conorii* and is prevalent in Mediterranean countries and Central Asia, including India.[78] Indian tick typhus and epidemic typhus could be the common subtypes seen in the South Indian population.[7]

Ocular involvement includes anterior segment features such as conjunctivitis, keratitis, and anterior uveitis. Retinitis, retinal vascular involvement, and optic disc changes are the most common ocular findings presenting with white retinal lesions, typically adjacent to retinal vessels and associated mild or moderate vitreous inflammation in 30% of patients with acute MSF. The cotton wool spot-like retinal lesions could result from intraretinal multiplication of organisms or alternatively as a result of immune complex deposition along retinal vessels.[78,79] Fluorescein angiography showed early hypofluorescence and late staining of large acute white retinal lesions and isofluorescence or moderate hypofluorescence of small active retinal lesions throughout the whole phase of dye transit. Optical coherence tomography shows serous retinal detachment and large foci of rickettsial retinitis which predominantly involves the inner retina.[78,79]

Balasundaram et al.[7] described a case series of patients with serologically proven Indian tick typhus (*R. conorii*) infection, in whom multifocal retinitis predominantly involved the posterior pole and macular involvement in the form of serous macular detachment or macular hard exudates. Doxycycline along with oral corticosteroids was effective in treating the condition. A case of bilateral *rickettsia*l retinitis was reported which worsened on systemic steroids and responded dramatically to therapy with oral doxycycline and steroid taper.[80] The authors' experience with 19 eyes of 10 patients with retinitis on the posterior pole with a recent history of fever with or without skin rash and a positive Weil-Felix test suggested a presumed rickettsial aetiology.[8]

PARASITE

Malaria

Malaria retinopathy is a condition which is a defining characteristic of cerebral malaria as a result of *Plasmodium falciparum* infection. This condition is usually bilateral and may be associated with papilloedema, patchy retinal whitening, focal changes in vessel colour, and white-centred haemorrhages.[81]

However, there have been studies that showed patients who were positive for malaria parasite,

Table 2: Summary of post fever uveoretinal sequalae as reported in published medical literature.

	Symptoms	Signs	OCT	FFA	Treatment
Dengue	Blurring of vision Scotoma Metamorphopsia Floaters[45]	Vitreous and retinal haemorrhages Posterior uveitis Optic neuritis and maculopathy Foveolitis[45] Macular oedema[15] RAPD Vessel engorgement Colour vision impairment Loss of contrast sensitivity[82] Intraretinal cystoid spaces Perifoveal telangiectasia Intraretinal haemorrhages[19,20] Cotton wool spots Microaneurysm[19,20] Retinitis Chorioretinitis Neuroretinitis[83] Roth spots Pan retinal vasculitis Exudative RD[82] Optic neuropathy[21]	Three patterns of maculopathy: diffuse retinal thickening, CME, and foveolitis[32-36] Diffuse retinal thickening: increased central or paracentral fovea thickness associated with loss of foveal dimple. CME: large intraretinal ovoid areas of hyporeflectivity with reflective septa separating the cystoid cavities. Foveolitis: area of thickening and high reflectivity at the subfoveal outer retina layer. There may be a tented elevation and separation of the highly reflective layer with accumulation of subretinal fluid. Serial OCT imaging demonstrate spontaneous rapid resolution of oedema.[12,38,40,41]	Arteriolar leakage Macular oedema Disc leakage Choroidal hyperfluoresence Blocked fluorescence or capillary non-perfusion Retinal vasculitis[39-41]	Oral corticosteroids (1 mg/kg) Standard supportive[13] care[12]
Chikungunya	Decreased vision Central scotoma Peripheral field defect Colour vision defect[84]	Intraretinal haemorrhages[2,33,44,78] Choroiditis Retinitis Optic neuritis[18] Neuroretinitis, and retrobulbar neuritis Panuveitis[84] Retinal oedema and opacification Mild vitritis Disc oedema Severe inflammation may result in exudative retinal detachment Retinal vasculitis Intermediate uveitis	Focal and multifocal patches of retinitis Macular oedema Serous detachment at the macula and localised involvement of the retinal vessel[1] Hyperreflectivity of OPL, ONL, disruption of ellipsoid zone, ELM, and interdigitation zone[85]	Early hyperfluorescence followed by late hyperfluorescence corresponding to area of retinitis[2,14]	Systemic acyclovir and prednisolone (40 mg/day orally for 1 week) tapered over a period of 6 weeks Topical 0.1% diclofenac[14] sodium four times a day
Zika	Decreased vision Redness Nonpurulent conjunctivitis[86]	Chorioretinal atrophy[52] Macular changes (thick pigment spots and/or chorioretinal atrophy with hyperpigmented ring) Optic nerve abnormalities (double ring hypoplasia, pallor, increased cup–disc ratio)[50,52,87] Macular pigment mottling Neuroretinal atrophy with macular involvement Iris coloboma Changes in retinal vasculature (congenital)[86]	Nodular elevations in the outer retinal layers Interruption of the outer retinal layers and an irregularity of the retinal pigment epithelial thickness[49-52]	Hypofluorescent in the centre of the macula Hyperfluorescent in the surrounding areas[50,51]	Intravenous methylprednisolone for 3 days, followed by oral prednisolone for 11 days[56]
Ebola	Ocular pain Photophobia Hyperlacrimation Foreign body sensation Red eye Progressive visual loss[61,62,88]	Vitreous opacities Vitritis Multiple chorioretinal scars with hypopigmented halos Small intraretinal haemorrhages Posterior uveitis Panuveitis[61,62]	Multiple vertical discontinuities of the ellipsoid zone and interdigitation zone with overlying v-shaped increased reflectance of the ONL[58]		Antiviral therapy with favipiravir[57,60] Periocular triamcinolone acetonide injection (40 mg/mL) Oral corticosteroids

Table 2 continued.

	Symptoms	Signs	OCT	FFA	Treatment
H1N1 (influenza A)	Severe bilateral vision loss to the level of light perception within 24 hours of having fever and myalgias Pain Redness[66,89]	Confluent ischaemic retinopathy Confluent and sharp-bordered ischemic retinal white patches[89] Dense anterior chamber inflammation Vitritis Peripheral retinal necrosis Choroiditis Submacular haemorrhages Macular oedema Neuroretinitis Vaso-occlusive retinal vasculitis[90] Frosted branch angiitis Exudative retinal detachment[91] Optic neuritis[92,93]	Inner retinal thickening and hyperreflectivity in both eyes; outer retinal layers were relatively spared[89]	Arteriolar occlusions posteriorly with minimal late leakage and no retinal vascular abnormalities in the periphery[89]	Oral corticosteroids[30]
West Nile fever	Blurring of vision Visual field defects Floaters Diplopia Redness Pain[69]	Active chorioretinal lesions appear as circular, deep, creamy lesions Inactive chorioretinal lesions appear partially atrophic and partially pigmented Multifocal chorioretinitis[69] Dense anterior chamber inflammation Vitritis Peripheral retinal necrosis Choroiditis Submacular haemorrhages Macular oedema Neuroretinitis Vaso-occlusive retinal vasculitis Frosted branch angiitis Exudative retinal detachment Optic neuritis Curvilinear clustering of whitish yellow chorioretinal scars with a 'target-like' appearance following the course of the retinal nerve fibres[67-69]	Inner retinal oedema in active inflammation and retinal atrophy in the late stage[67]	Active chorioretinal lesions: early hypofluorescence and late staining Inactive lesions:central hypofluorescence and peripheral ring-like hyperfluorescence[67-69]	Supportive care[68,69]
Typhoid	Decreased vision RAPD Colour vision defect	Disc pallor Vasculitis Multiple whitish fluffy areas of deep retinitis[16,74,76] Large neurosensory detachment in the macular area. Cotton-wool spot Retinal venous sheathing	Highly reflective and disorganised inner retinal layer Serous retinal detachment		Prednisolone (1 mg/kg body weight/day) Steroids tapered over 2 months with regular monitoring[5]
Rickettsiosis	Diminished vision	Soft exudates Retinal haemorrhages[7,8,22] Retinal whitening	Vitreous cells Neurosensory detachment		Oral doxycycline Oral prednisolone[7,8,22]

CME: cystoid macular oedema; ELM: external limiting membrane; FFA: fundus fluorescein angiography; OCT: optical cohorence tomography; ONL: outer nuclear layer; OPL: outer plexiform layer; RAPD: relative afferent pupillary defect; RD: retinal detachment.

had a unilateral large retinitis patch with vascular sheathing, and relative afferent pupillary defect with no evidence of cerebral malaria.[1] Table 2 summaries the clinical features seen in PFURS.

Management

Treatment of arbovirus infection (dengue fever, chikungunya, Zika virus, WNV, and yellow fever) is essentially symptomatic because there are currently no effective antiviral treatments.[94]

Steroids are the mainstay of treatment in patients who are persistently symptomatic and have poor vision as a result of ocular complications of PFURS.[1-9,14,15] In one case series, all patients with post fever retinitis were treated with oral prednisolone at 1 mg/kg body weight irrespective of aetiology, and the steroids were tapered based on clinical response over a period of 6 weeks; all patients had improvement in vision, despite the differences in aetiology.[1,14] Oral doxycycline and/or acyclovir or valacyclovir can be started empirically while investigations are awaited.[2] Other modalities of treatment are intravenous methylprednisolone, posterior sub-Tenon's injection, intravitreal triamcinolone, intravitreal anti-VEGF injections (bevacizumab or ranibizumab).[2]

However, a large number of patients have self-limiting disease and resolve spontaneously without any treatment. Some case reports and case series have documented successful conservative management, hence it is believed to be a self-limiting condition.[1,32] Even though spontaneous recovery is possible in post febrile neuroretinitis, steroids help in hastening the resolution of retinitis and improving the vision, thus decreasing the time to recovery.[76] Whereas, another report by the present authors mentioned successful treatment of macular oedema and retinitis without steroids.[77]

CONCLUSION

Post fever retinitis of almost all aetiologies present with a similar morphological pattern because the condition manifests approximately 3 weeks after onset of fever and follows a preset natural course before resolution. These manifestations, which generally constitute inner retinitis at the posterior pole with or without optic nerve involvement, may be the result of a direct invasion by the pathogen or by indirect invasion mediated through immune-modulated mechanisms. It resolves in all cases without any relapses, but visual prognosis varies depending on macular ischaemic damage and optic nerve involvement. No specific treatment seems to be established based on the literature and patients may improve as a part of natural history of the disease process. However, some studies highlighted the need for a high index of suspicion by an ophthalmologist to diagnose this entity and for the early introduction of steroids for rapid improvement in symptoms and prevention of vision loss. Early referral to an ophthalmologist by the treating physician would result in a better functional outcome for the patients. This entity needs to be studied further to understand the detail of the natural history and histopathological and immunological aides. Further studies are needed to elucidate the mechanism of ophthalmic complications of viral, bacterial, and parasitic fevers.

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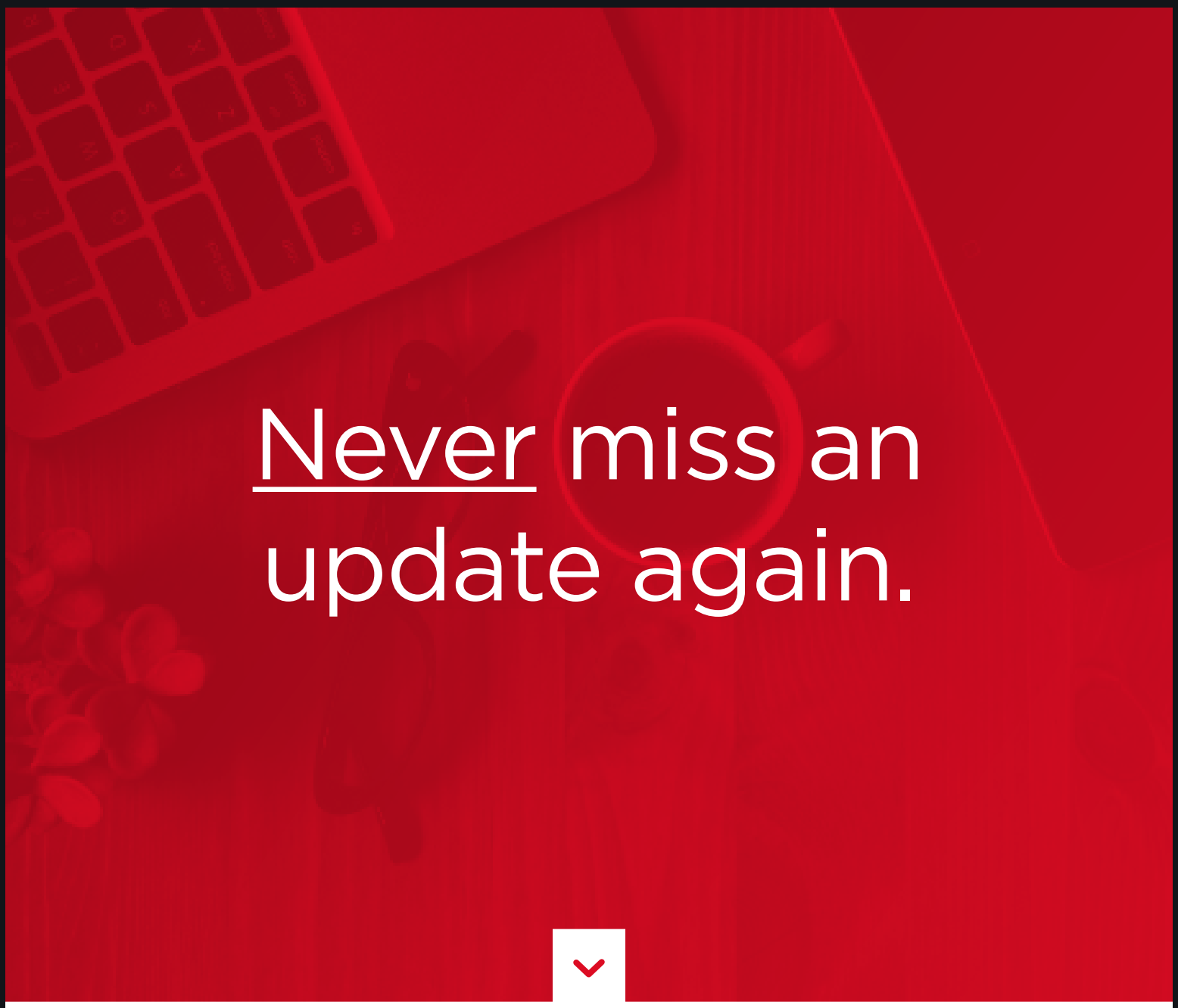

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