The Turkish Journal of Pediatrics 2024; 66: 637-642
https://doi.org/10.24953/turkjpediatr.2024.4902

Case Report

Changes in skin barrier integrity by electrical impedance spectroscopy during dupilumab treatment on a child with severe atopic dermatitis

Elif Yaycı[1], Işıl Ezelsoy[1], Beliz Su Gündoğdu[1], Betül Büyüktiryaki[2], Cansın Saçkesen[2]

[1]School of Medicine, Koç University, İstanbul; [2]Department of Pediatrics, Division of Pediatric Allergy, School of Medicine, Koç University, İstanbul, Türkiye.

ABSTRACT

Background. Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by epidermal skin barrier dysfunction and altered immune response. Electrical impedance spectroscopy (EIS) has been used as a novel tool to detect skin barrier changes in AD. EIS is a non-invasive measure of the electrical impedance of tissue and is sensitive to cellular structure and extracellular environment.

Case Presentation. An 8-year-old girl presented with severe AD, starting at 3 years of age. She also had allergic rhinitis, food allergies, and sensitization to mites, eggs, and nuts. Unresponsive to other treatments, she was administered 300 mg of dupilumab, a monoclonal antibody inhibiting IL-4 and IL-13 activity. Patient's response to the treatment and skin barrier integrity was followed for 6 months: First at the baseline (before dupilumab) and then again at the 1st, 2nd, 3rd, and 5.5th month after dupilumab with SCORing Atopic Dermatitis (SCORAD), as well as measurements of moisture by MoistureMeterSC (Delfin®) and EIS by Nevisense® (SciBase) on the forearm and antecubital fossa of the same arm. At the end of 6 months, her SCORAD improved from 96 to 37. The moisture measurements were variable. The EIS by Z1 score in the forearm increased from 72 to 141 and EIS by MIX scores increased from 2.7 to 6.2. The correlation between SCORAD and forearm EIS by Z1 and MIX scores were significant: r=-0.913, (p=0.03) and r=-0.881, (p=0.049). The correlation between forearm MIX scores with sleeplessness and itching was significant: r=-0.956, (p=0.011), r=-0.942, (p=0.017).

Conclusion. As higher EIS scores reflect stronger barrier integrity, the increase in Z1 and MIX obtained from Nevisense® implies an improvement in the skin barrier integrity during dupilumab treatment. This report highlights the potential use of EIS in atopic dermatitis patients to evaluate treatment efficacy. We urge rapid and non-invasive use of EIS in pediatrics to be further investigated in clinical settings.

Key words: atopic dermatitis, children, electric impedance spectroscopy, epithelium, dupilumab.

Atopic dermatitis (AD) is a chronic inflammatory skin disorder with heterogeneous pathophysiology. Skin epithelial barrier dysfunction is one of the most important components of AD. Defects in the epithelial barrier increase transcutaneous water loss and allow microbial dysbiosis.[1-3] Th-2 mediated immune response is accentuated in AD, contributing to inflammatory changes. Th-2 cytokines interleukin (IL)-4 and IL-13 influence

✉ Cansın Saçkesen ▪ csackesen@ku.edu.tr

Received 30th Jun 2024, revised 12th Aug 2024, accepted 30th Sep 2024.

The study has been previously presented as a poster in World Immune Regulation Meeting XVII, 5-8 July 2023, Davos, Switzerland.

keratinocyte function and increase the epidermal barrier damage. They are also responsible for IgE production, T cell activation, and eosinophil recruitment.[1-3] While AD management depends on AD severity, inhibition of Th-2 cytokines via targeting the IL-4Ra receptor is introduced as one of the treatment models for AD. Dupilumab, a monoclonal antibody against IL-4Ra, has been well tolerated and shown to decrease AD severity significantly.[4] Furthermore, Berdyshev et al. reported improved skin barrier function by dupilumab with transepidermal water loss measurements and stratum corneum ceramide composition analysis in adults and adolescents.[5]

A new method proposed to evaluate epidermal integrity in atopic dermatitis is electrical impedance spectroscopy (EIS).[6-8] EIS is a non-invasive measure of a tissue's electrical resistance against alternating currents with different frequencies. Nevisense® (Scibase) device measures electrical impedance at 35 different frequencies along 1 kHz and 2.5 MHz intervals at 4 different depths in 10 permutations. It collects 700 data points. The applied voltage is 150 mV, and the current is 75 μA, which is undetectable by the patient.[6,7] EIS is sensitive to cell structure, compactness, and extracellular environment characteristics such as water and lipid content. EIS is approved for diagnosis and differentiation of skin cancers from benign lesions.[7] Rinaldi et al. used EIS to detect skin barrier defects of mice epidermal barrier damaged by proteases, cholera toxin, and tape stripping, where they confirmed the damage by RT-PCR and histological analysis.[8] Recent studies used EIS-based algorithms to differentiate between the skin of AD patients and healthy people in adults and pediatrics.[6,7] Consequently, we aimed to investigate the skin epidermal integrity during dupilumab treatment in a pediatric patient using EIS and moisture measurements.

Case presentation

Here, we present an 8-year-old female patient with severe AD starting at the age of three years. She also has egg allergy, nut allergy, and allergic rhinitis with sensitization to mites. The patient is on an elimination diet for eggs and nuts and uses special measures to reduce mite exposure including bedsheets for the mite allergy. Patient history does not have recurrent infections, otitis, pneumonia, or abscesses, excluding the immunodeficiency diagnosis. In her initial laboratory tests, total IgE was 6006 IU/L, and eosinophil count was 1210 (14.6%). Due to high eosinophilia, IgE levels, and persistent severe atopic dermatitis, hypereosinophilia, hyper-IgE syndromes, and other immune regulation disorders with genetic mutations and IgG, IgA, IgM, vaccine serology, lymphocyte subset groups analysis by flow cytometry have all been investigated. However, these tests were negative. She was treated with regular topical corticosteroids (CS), topical calcineurin inhibitors (pimecrolimus and tacrolimus), and intermittent oral CS. Since she was unresponsive to the treatment, cyclosporine 4 mg/kg/day was started as an immunosuppressive therapy. However, severe AD persisted, and cyclosporine treatment was discontinued due to side effects (e.g., tremor and nausea). Following this, 300 mg/month of omalizumab, a monoclonal anti-IgE antibody, was administered. Omalizumab did not improve her AD lesions, and she experienced myalgia. After 2 months of omalizumab treatment, 300 mg dupilumab treatment was initiated, followed by a second dose 2 weeks later. Then, 300 mg of dupilumab was given monthly. During dupilumab treatment, the patient continued to use moisturizer creams daily. To ensure greater improvements in atopic dermatitis progression, topical corticosteroid was continued when there were atopic dermatitis flare-ups.

During six months of dupilumab treatment, the patient's response to treatment was followed by EIS and skin moisture measurements. The first measurement was collected before dupilumab treatment and recorded as the baseline. The other 4 measurements were obtained at the 1st, 2nd, 3rd, and 5.5th months of dupilumab treatment. To date, the patient has not experienced any adverse events with dupilumab treatment.

At each visit, SCORing Atopic Dermatitis (SCORAD), including self-reported sleeplessness and itching, were recorded for AD severity. Skin moisture measurements and EIS measurements were taken from 2 different sites each time. The first site, the forearm, is the clinically unaffected skin. Throughout the investigation, there was no active lesion in the forearm. In the second site, antecubital fossa, the patient had clinically active lesions. Triplicates of skin moisture measurement were taken from the volar forearm and antecubital fossa of the same arm using MoistureMeterSC® (Delfin Technologies, Kuopio, Finland). The average of triplicates was used as the final moisture measurement. Then, EIS measurements were collected in duplicates from the same areas using Nevisense®. To collect EIS measurements, the site was moistened with physiological saline for 30 seconds before applying the electrode. Z1 and MIX values obtained from Nevisense® were used as EIS scores. Z1, contact impedance, is the "mean value of all permutations for the amplitude at 1 kHz" whereas MIX is "the mean value of all permutations for the slope of the amplitude curve between 20-500 kHz".[9] Compared to Z1, the MIX score reflects the barrier function of deeper layers.[10] Importantly both scores are positively correlated with skin barrier function. The average of multiplicate measurements was used as final scores for Z1 and MIX.

After 6 months of dupilumab treatment, the pronounced improvement in her AD was marked by the reduction of her SCORAD score from 96.15 to 37.65. Her sleeplessness and itching scores reduced from 10 to 2 and 4, respectively. The average of skin moisture measurements in her volar forearm increased in earlier months of treatment but then returned to a baseline measurement (6.3) in the last (6.1) month. In the antecubital fossa, skin moisture measurements were 5.1 for the baseline and 13.3 for the final month. In the volar forearm, both final average Z1 (141.6) and final average MIX (6.2) scores were higher than baseline (Z1:72.5, MIX:2.7). All measurements are summarized in Table I.

Correlations between EIS scores, skin moisture scores, and SCORAD were evaluated by 2-tailed Pearson tests in SPSS. Forearm Z1 (r=-0.913, p=0.03) and forearm MIX scores (r=-0.881, p=0.049) had a significant inverse correlation with SCORAD values (Fig. 1a, 1b). The correlation between forearm MIX scores with sleeplessness and itching was significant: r=-0.956 (p=0.011), r=-0.942 (p=0.017) (Fig. 1c, 1d). However, no significant correlation was found between SCORAD and antecubital skin moisture measurements and antecubital EIS measurements. An informed consent was obtained from the parents for the publication of this case report.

Table I. Summary of all measurements.

	SCORAD	Sleeplessness	Itching	Z1 (EIS) Forearm	MIX (EIS) Forearm	Skin moisture Forearm	Z1 (EIS) Antecubital fossa	MIX (EIS) Antecubital fossa	Skin moisture Antecubital fossa
Before dupilumab	96.1	10	10	72.5	2.6	6.3	179.9	5.1	5.1
1st month of dupilumab	57.3	4	5	93.5	5.8	17.4	169.6	10.1	11.0
2nd month of dupilumab	63.1	4	5	99.6	6.5	11.5	176.0	8.7	16.0
3rd month of dupilumab	47.2	3	6	113.2	6.2	6.3	63.6	6.0	8.9
5.5th month of dupilumab	37.6	2	4	141.6	6.2	6.1	118.9	7.3	13.3

EIS, electrical impedence spectroscopy; SCORAD, SCORing Atopic Dermatitis.

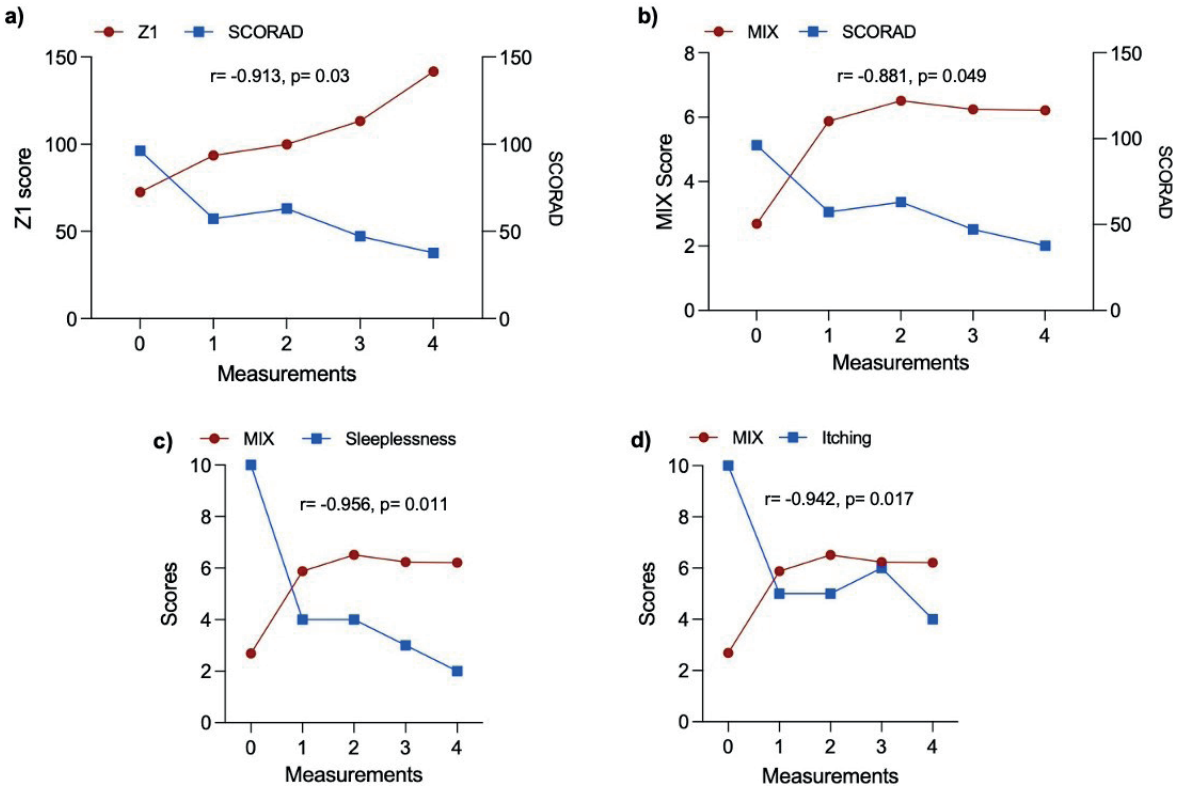

Fig. 1. Progression of forearm EIS scores with other severity score assessment during dupilumab treatment **a)** forearm EIS-Z1 scores with SCORAD, **b)** forearm EIS-MIX scores with SCORAD, **c)** forearm EIS-MIX scores with itching, and **d)** forearm EIS-MIX scores with sleeplessness. Measurement 0 represents the baseline, and measurements 1, 2, 3, and 4 represent the 1st, 2nd, 3rd, and 5.5th month of treatment, respectively. EIS, electrical impedence spectroscopy; SCORAD, SCORing Atopic Dermatitis.

Discussion

Dupilumab efficacy in atopic dermatitis in children and adults has been well-acknowledged.[5,11,12] In accordance, the patient's SCORAD decreased by 56%. In the literature, Dupilumab has been found to improve the skin epithelial barrier by using skin biopsies. After dupilumab treatment, skin biopsies of atopic dermatitis patients have been found to reduce type-2 inflammation activity and increase the expression of epidermal differentiation barrier genes and lipid metabolism genes.[13] This report investigated the effect of dupilumab using non-invasive methods. Comparing the moisture, itchiness, sleeplessness, and SCORAD; the MIX score in the volar forearm showed the highest change in the first month of the dupilumab treatment. MIX score in the volar forearm noted a 223% increase, while the Z1 score increased by 129%. Since higher EIS scores (Z1 and MIX) reflect stronger skin barrier activity, an improving trend in EIS scores on the forearm may imply an improvement in skin epithelial barrier integrity during dupilumab treatment. Sasaki et al. demonstrated EIS's ability to differentiate between atopic dermatitis and healthy skin in children for the first time.[7] In another study, EIS measurements reflected skin barrier healing after 3 weeks of hospitalization for AD treatment in adult atopic dermatitis patients.[6] Yet, literature on the use of EIS in the evaluation of atopic dermatitis treatments in children is lacking. This case report highlights EIS's association with improved barrier function in a child after AD treatment for the first time.

The main variables EIS is influenced by are skin hydration, SC thickness, and cellular properties. EIS can be affected by the age of the participants.[10] While one study did not find any association between topical cream use and EIS measurement, a recent study investigating factors affecting EIS and transepidermal water loss measurements concluded that EIS is sensitive to the use of cream ointment and skin washing up to 90 minutes.[7,10] Sweating or prior exercise did not change EIS measurements.[10] In this patient, the differences in EIS scores in the volar forearm and antecubital fossa may be attributed to anatomic location and clinical severity of the skin. EIS measurements may vary according to the location of the measurement because of the different composition of the skin. Furthermore, Rinaldi et al. demonstrated significantly different EIS values in lesional areas compared to non-lesional measurements.[6] The patient had severe AD lesions in the antecubital fossa with lichenification, excoriation, and oozing. Because of these severe lesions in the antecubital area, EIS scores in the antecubital fossa are expected to be different from the scores obtained in the unaffected forearm area. Measurements from the same site may be affected by topical cream use and skin washing.[10] The patient used the topical creams on antecubital fossa variably which may have resulted in inconsistent progression of EIS scores in antecubital fossa along the dupilumab treatment.

While the use of scoring tools like SCORAD is well validated for clinical studies, the nature of scoring systems has its limitations due to intraobserver and interobserver variability.[14,15] EIS measurements can be standardized to have reliable and reproducible assessment of AD, supporting evidence-based medicine. Furthermore, SCORAD and other scoring tools aim to describe AD severity through present clinical symptoms while EIS differentiates between non-lesional skin of AD patients and healthy controls.[7] By evaluating the overall skin epithelial barrier status, EIS provides a more profound perspective for the assessment of treatment efficacy. To our knowledge, this is the first case to show skin barrier changes by dupilumab treatment using EIS changes in a pediatric patient. Rapid and non-invasive, EIS seems to be a potential objective tool to assess dupilumab efficacy at the very early stage of treatment by evaluating skin barrier dysfunction.

Acknowledgements

The authors gratefully acknowledge use of the services and facilities of the Koç University Research Center for Translational Medicine (KUTTAM), funded by the Republic of Turkey Ministry of Development. The content is solely the authors' responsibility and does not necessarily represent the official views of the Ministry of Development.

Ethical approval

Informed consent from parents of the patient is obtained for the publication of this case report.

Author contribution

The authors confirm contribution to the paper as follows: study conception and design: CS; data collection: EY, IE, BSG; data analysis and interpretation: EY, BB, CS; draft manuscript preparation: EY, BB, CS; critical review of the manuscript: IE, BSG, BB, CS. All authors reviewed the results and approved the final version of the article.

Source of funding

The authors declares the study received no funding.

Conflict of interest

The authors declares that there is no conflict of interest.

REFERENCES

1. Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. Nat Rev Dis Primers 2018; 4: 1. https://doi.org/10.1038/s41572-018-0001-z
2. Peng W, Novak N. Pathogenesis of atopic dermatitis. Clin Exp Allergy 2015; 45: 566-574. https://doi.org/10.1111/cea.12495
3. David Boothe W, Tarbox JA, Tarbox MB. Atopic dermatitis: pathophysiology. Adv Exp Med Biol 2017; 1027: 21-37. https://doi.org/10.1007/978-3-319-64804-0_3
4. Harb H, Chatila TA. Mechanisms of dupilumab. Clin Exp Allergy 2020; 50: 5-14. https://doi.org/10.1111/cea.13491
5. Berdyshev E, Goleva E, Bissonnette R, et al. Dupilumab significantly improves skin barrier function in patients with moderate-to-severe atopic dermatitis. Allergy 2022; 77: 3388-3397. https://doi.org/10.1111/all.15432
6. Rinaldi AO, Korsfeldt A, Ward S, et al. Electrical impedance spectroscopy for the characterization of skin barrier in atopic dermatitis. Allergy 2021; 76: 3066-3079. https://doi.org/10.1111/all.14842
7. Sasaki M, Sundberg M, Frei R, et al. Electrical impedance spectroscopy detects skin barrier dysfunction in childhood atopic dermatitis. Allergy 2024; 79: 142-152. https://doi.org/10.1111/all.15895
8. Rinaldi AO, Morita H, Wawrzyniak P, et al. Direct assessment of skin epithelial barrier by electrical impedance spectroscopy. Allergy 2019; 74: 1934-1944. https://doi.org/10.1111/all.13824
9. SciBase. Nevisense Clinical Reference Guide. 2014. Article Number: 975-0009-04. Available at: https://scibase.com/wp-content/uploads/2017/11/Clinical-Reference-Guide-1.pdf
10. Huygen L, Thys PM, Wollenberg A, Gutermuth J, Krohn IK. Skin barrier function assessment: electrical impedance spectroscopy is less influenced by daily routine activities than transepidermal water loss. Ann Dermatol 2024; 36: 99-111. https://doi.org/10.5021/ad.23.052
11. Paller AS, Siegfried EC, Thaçi D, et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: a randomized, double-blinded, placebo-controlled phase 3 trial [published correction appears in J Am Acad Dermatol 2021; 84: 230]. J Am Acad Dermatol 2020; 83: 1282-1293. https://doi.org/10.1016/j.jaad.2020.06.054
12. Cork MJ, Thaçi D, Eichenfield LF, et al. Dupilumab safety and efficacy in a phase III open-label extension trial in children 6-11 years of age with severe atopic dermatitis. Dermatol Ther (Heidelb) 2023; 13: 2697-2719. https://doi.org/10.1007/s13555-023-01016-9
13. Guttman-Yassky E, Bissonnette R, Ungar B, et al. Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. J Allergy Clin Immunol 2019; 143: 155-172. https://doi.org/10.1016/j.jaci.2018.08.022
14. de Bruin Weller MS, Knulst AC, Meijer Y, Bruijnzeel-Koomen CAFM, Pasmans SGM. Evaluation of the child with atopic dermatitis. Clin Exp Allergy 2012; 42: 352-362. https://doi.org/10.1111/j.1365-2222.2011.03899.x
15. Oranje AP, Glazenburg EJ, Wolkerstorfer A, de Waard-van der Spek FB. Practical issues on interpretation of scoring atopic dermatitis: the SCORAD index, objective SCORAD and the three-item severity score. Br J Dermatol 2007; 157: 645-648. https://doi.org/10.1111/j.1365-2133.2007.08112.x