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DARIEROVA BOLEST – RETROSPEKTIVNI PRIKAZ 67 SLUČAJEVA

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SAŽETAK

Uvod/cilj: Darierova bolest predstavlja retku autozomno dominantnu genodermatozu uzrokovanu mutacijama gena ATP2A2, sa karakterističnim kliničkim i histopatološkim nalazima. Cilj ovog rada bio je prikaz epidemioloških i terapijskih karakteristika pacijenata sa Darierovom bolešću lečenih u tercijarnoj ustanovi tokom petnaestogodišnjeg perioda.

Metode: Sprovedena je retrospektivna kohortna studija koja je obuhvatila 67 pacijenata sa dijagnozom Darierove bolesti lečenih na Klinici za dermatovenerologiju Univerzitetskog kliničkog centra Srbije u Beogradu. Dijagnoza je postavljena na osnovu karakteristične kliničke slike i histopatološke verifikacije. Analizirani su epidemiološki, klinički i terapijski parametri pacijenata.

Rezultati: U ispitivanoj grupi zabeležena je predominacija ženskog pola (66%), dok su se prve kožne promene najčešće javljale tokom adolescencije i rane odrasle dobi. Pozitivna porodična anamneza registrovana je kod 48% pacijenata, što potvrđuje autozomno dominantni obrazac nasleđivanja. Promene su dominantno bile lokalizovane na trupu (85%). Neuropsihijatrijski komorbiditeti evidentirani su kod 16% ispitanika. Lokalna terapija primenjivana je kod svih pacijenata, dok su sistemski retinoidi korišćeni kod 51% pacijenata, uglavnom kod generalizovanih formi bolesti.

Zaključak: Rezultati ukazuju na hroničan tok bolesti, izraženu fenotipsku varijabilnost i potrebu za individualizovanim terapijskim pristupom.

Ključne reči: Darierova bolest, genodermatoza, epidemiologija, terapija

Uvod

Darierova bolest (eng. *Morbus Darier*), poznata i kao folikularna diskeratoza (lat. *dyskeratosis follicularis*), predstavlja retku autozomno dominantnu genodermatozu uzrokovanu mutacijama gena ATP2A2, koji kodira sarko/endoplazmatsku retikulum Ca^{2+}-ATPazu tipa 2 (SERCA2) (1,2). Poremećaj intracelularne homeostaze kalcijuma dovodi do akantolize i diskeratoze, što se klinički manifestuje hiperkeratotičnim papulama dominantno lokalizovanim u seboroičnim regijama (1).

Prevalencija bolesti procenjuje se na 1:30.000 do 1:100.000, uz podjednaku zastupljenost oba pola u većini populacionih studija (1,3). Iako je penetrantnost visoka, fenotipska ekspresivnost je izrazito varijabilna, čak i unutar iste porodice (4,5).

Pored kutanih manifestacija, sve je više podataka o sistemskim i neuropsihijatrijskim komorbiditetima, uključujući epilepsiju i neurodegenerativne poremećaje (6), srčanu insuficijenciju (7) i metaboličke poremećaje (8), što dodatno naglašava značaj sveobuhvatnog pristupa pacijentima sa Darierovom bolešću.

Cilj rada bio je prikaz epidemioloških i terapijskih karakteristika pacijenata sa Darierovom bolešću lečenih u tercijarnoj ustanovi tokom petnaestogodišnjeg perioda.

Metode

Sprovedena je retrospektivna kohortna studija koja je obuhvatila 67 pacijenata sa dijagnozom Darierove bolesti lečenih na Klinici za dermatovenerologiju Univerzitetskog kliničkog centra Srbije u Beogradu. Analizirana je medicinska dokumentacija pacijenata pregledanih tokom 2020. godine, u periodu pandemije COVID-19.

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DARIER DISEASE –A RETROSPECTIVE SERIES OF 67 CASES

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SUMMARY

Introduction/Aim: Darier disease is a rare autosomal dominant genodermatosis caused by mutations in the ATP2A2 gene and characterized by distinct clinical and histopathological findings. The aim of this study was to present the epidemiological and therapeutic characteristics of patients with Darier disease treated at a tertiary care center over a fifteen-year period.

Methods: A retrospective cohort study including 67 patients diagnosed with Darier disease and treated at the Clinic of Dermatovenereology, University Clinical Center of Serbia, Belgrade, Republic of Serbia, was conducted. The diagnosis was established based on characteristic clinical presentation and histopathological confirmation. Epidemiological, clinical, and therapeutic characteristics were analyzed.

Results: Female predominance (66%) was observed in the study population, while the first skin lesions most commonly appeared during adolescence and early adulthood. Positive family history was recorded in 48% of patients, supporting the autosomal dominant inheritance pattern. Lesions were predominantly localized on the trunk (85%). Neuropsychiatric comorbidities were observed in 16% of patients. Topical therapy was used in all patients, whereas systemic retinoids were administered in 51% of patients, predominantly in generalized forms of the disease.

Conclusion: The results highlight the chronic course of the disease, marked phenotypic variability, and the need for individualized therapeutic approaches.

Keywords: Darier disease, genodermatosis, epidemiology, therapy

Introduction

Darier disease, also known as *dyskeratosis follicularis* is a rare autosomal dominant genodermatosis caused by mutations in the ATP2A2 gene, which encodes sarco/endoplasmic reticulum Ca^2 – ATPase type 2 (SERCA2) (1,2). The disruption in intracellular calcium homeostasis leads to acantholysis and dyskeratosis, which is clinically manifested by hyperkeratotic papules predominantly localized in seborrheic areas (1).

The prevalence of this disease is estimated between 1:30,000 and 1:100,000, with equal representation of both sexes in most population studies (1,3). Although penetrance is high, phenotypic expressivity is highly variable, even within the same family (4,5).

In addition to cutaneous manifestations, there are more and more data on systemic and neuropsychiatric comorbidities, including epilepsy and neurodegenerative disorders (6), heart failure (7) and metabolic disorders (8), which further emphasizes the significance of a comprehensive approach to patients with Darier disease.

The aim of this study was to present the epidemiological and therapeutic characteristics of patients with Darier disease treated at a tertiary care center over a fifteen-year period.

Methods

A retrospective cohort study that included 67 patients diagnosed with Darier disease and treated at the Clinic of Dermatovenereology, University Clinical Center of Serbia, Belgrade, Republic of Serbia, was conducted. The medical records of patients, who were examined in 2020, during the COVID-19 pandemic, were analyzed.

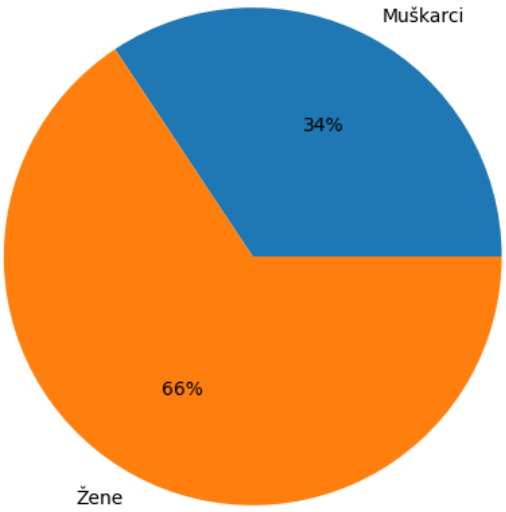
Dijagnoza Darierove bolesti postavljena je na osnovu karakteristične kliničke slike i histopatološke verifikacije. Iz istorija bolesti prikupljeni su podaci o polu, uzrastu pri pojavi prvih simptoma, porodičnoj anamnezi, lokalizaciji promena, prisustvu komorbiditeta i primenjenim terapijskim modalitetima. Podaci su obrađeni metodom deskriptivne statistike i prikazani kao apsolutne i relativne frekvencije. Istraživanje je sprovedeno u skladu sa principima Helsinške deklaracije i odobreno od strane Etičkog odbora Univerzitetskog kliničkog centra Srbije (broj odluke: 65143/2020-EO).

Rezultati

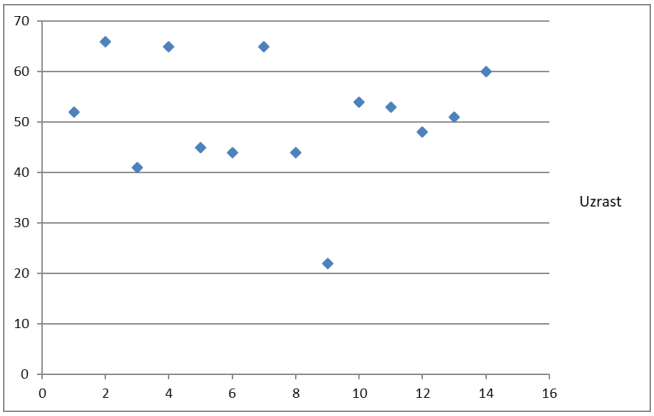
Od ukupno 67 ispitanika sa Darierovom bolešću, ženskog pola bilo je 44 (66%), a muškog 23 (34%) (grafikon 1). Prve kožne promene javile su se kod 76% ispitanika tokom prve tri decenije života, najčešće u periodu puberteta (grafikon 2). Pozitivna porodična anamneza registrovana je kod 48% pacijenata, dok je negativna porodična anamneza zabeležena kod 52% ispitanika (grafikon 3).

Kožne promene bile su dominantno lokalizovane na trupu (85%) (slika 1). Na osnovu kliničke prezentacije, klasični generalizovani oblik bolesti bio je prisutan kod 97% pacijenata, dok su linearni i bulozni oblici registrovani kod po 1,5% ispitanika (grafikon 4).

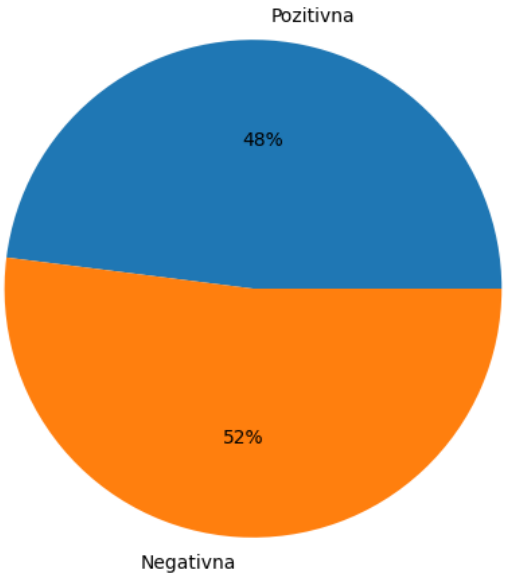
Grafikon 1. Polna distribucija ispitanika sa Darierovom bolešću



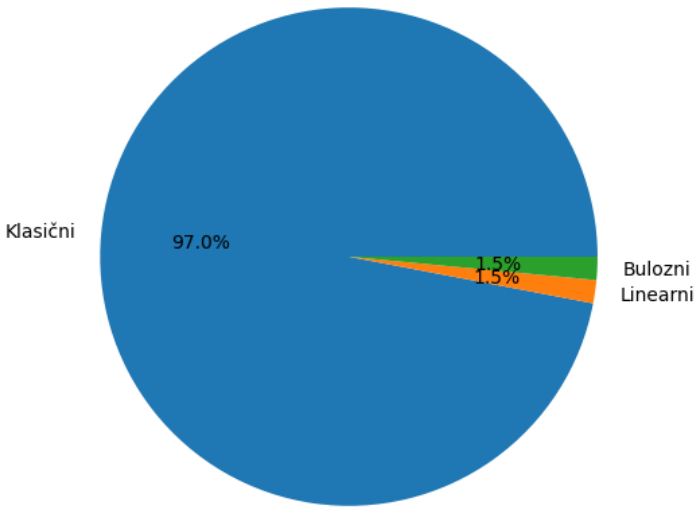
Grafikon 2. Starosna distribucija ispitanika sa Darierovom bolešću



Grafikon 3. Distribucija ispitanika sa Darierovom bolešću prema porodičnoj anamnezi



Grafikon 4. Distribucija ispitanika sa Darierovom bolešću prema tipu bolesti



The diagnosis of Darier disease was established based on characteristic clinical presentation and histopathological confirmation. Data on gender, age at the onset of the first symptoms, family history, localization of changes, presence of comorbidities and applied therapeutic modalities were collected. Data were analyzed using the method of descriptive statistics and presented as absolute and relative frequencies. The study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of University Clinical Center of Serbia (decision number: 65143/2020-EO).

Results

Out of 67 patients with Darier disease, 44 (66%) were women, while 23 (34%) were men (Figure 1). The first skin lesions appeared in 76% of participants during the first three decades of life, most often during puberty (Figure 2). Positive family history was recorded in 48% of patients, while negative family history was recorded in 52% of patients (Figure 3).

Skin lesions were predominantly localized on the trunk (85%) (Figure 1). Based on the clinical presentation, the classic generalized form of the disease was present in 97% of patients, while the linear and bullous presentations were recorded in 1.5% of patients (Figure 4).

Figure 1. Sex distribution of patients with Darier disease

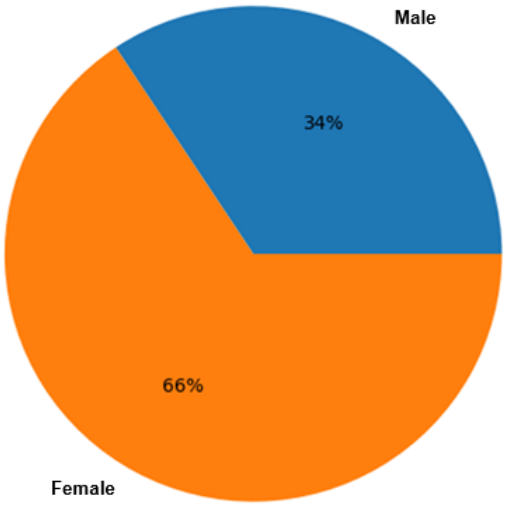


Figure 2. Age distribution at disease onset in patients with Darier disease

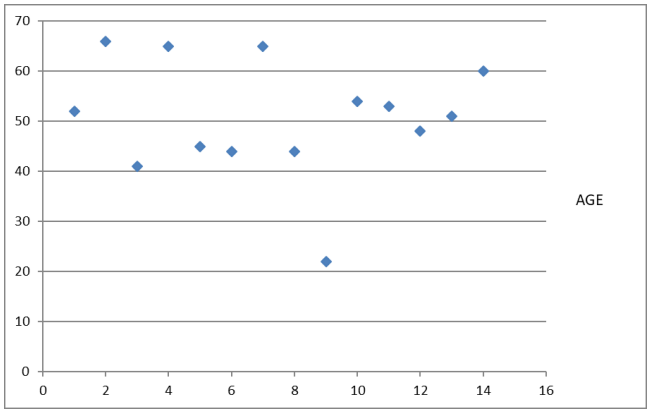


Figure 3. Family history distribution in patients with Darier disease

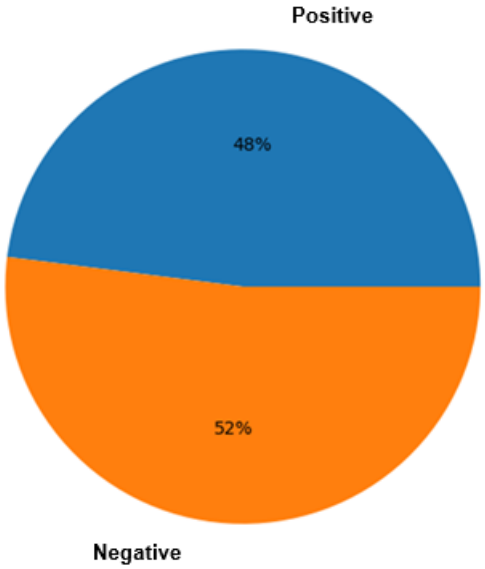
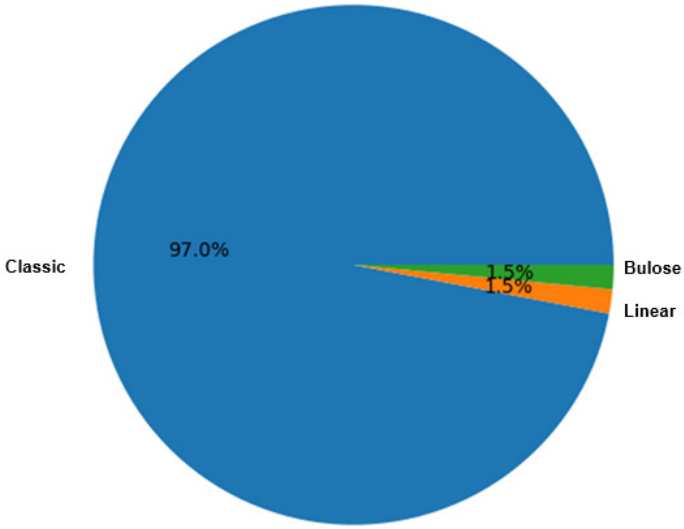
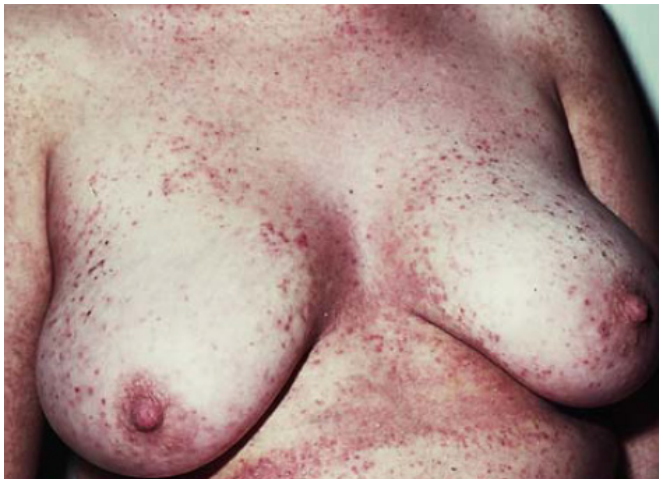


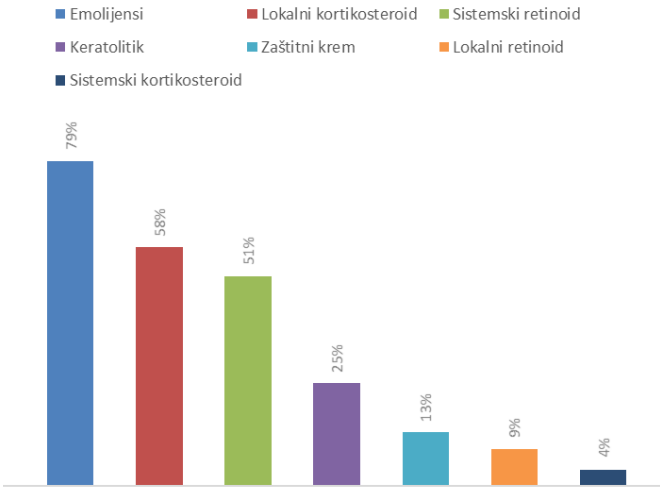
Figure 4. Distribution of clinical forms of Darier disease



Slika 1. Karakteristične hiperkeratotične papule u tipičnoj distribuciji (presternalno i submamarno) kod pacijentkinje sa Darierovom bolešću



Grafikon 6. Distribucija ispitanika sa Darierovom bolešću prema vrsti terapije



Analiza lokalizacije lezija pokazala je dominantnu zahvaćenost seboroičnih regija, pre svega trupa, vrata i ekstremiteta (grafikon 5). Neuropsihijatrijski komorbiditeti evidentirani su kod 16% ispitanika.

Lokalna terapija primenjivana je kod svih pacijenata, najčešće u vidu emolijensa (79%) i lokalnih kortikosteroida (58%). Sistemski retinoidi korišćeni su kod 51% pacijenata, uglavnom kod generalizovanih i klinički izraženijih formi bolesti (grafikon 6).

Diskusija

Rezultati naše retrospektivne serije slučajeva potvrđuju da se *Morbus Darier* najčešće manifestuje u adolescenciji i ranoj odrasloj dobi, što je u skladu sa kliničkim opisima iz savremenih pregleda literature. Takagi i sar. (1) navode da se prve lezije u najvećem broju slučajeva javljaju tokom druge decenije života, dok Ettinger i sar. (3) potvrđuju da se bolest tipično ispoljava u pubertetu, uz hroničan i relapsno-remitentni tok. Naši podaci, prema kojima

Grafikon 5. Učestalost lokalizacije Darierove bolesti na predilekcionim mestima

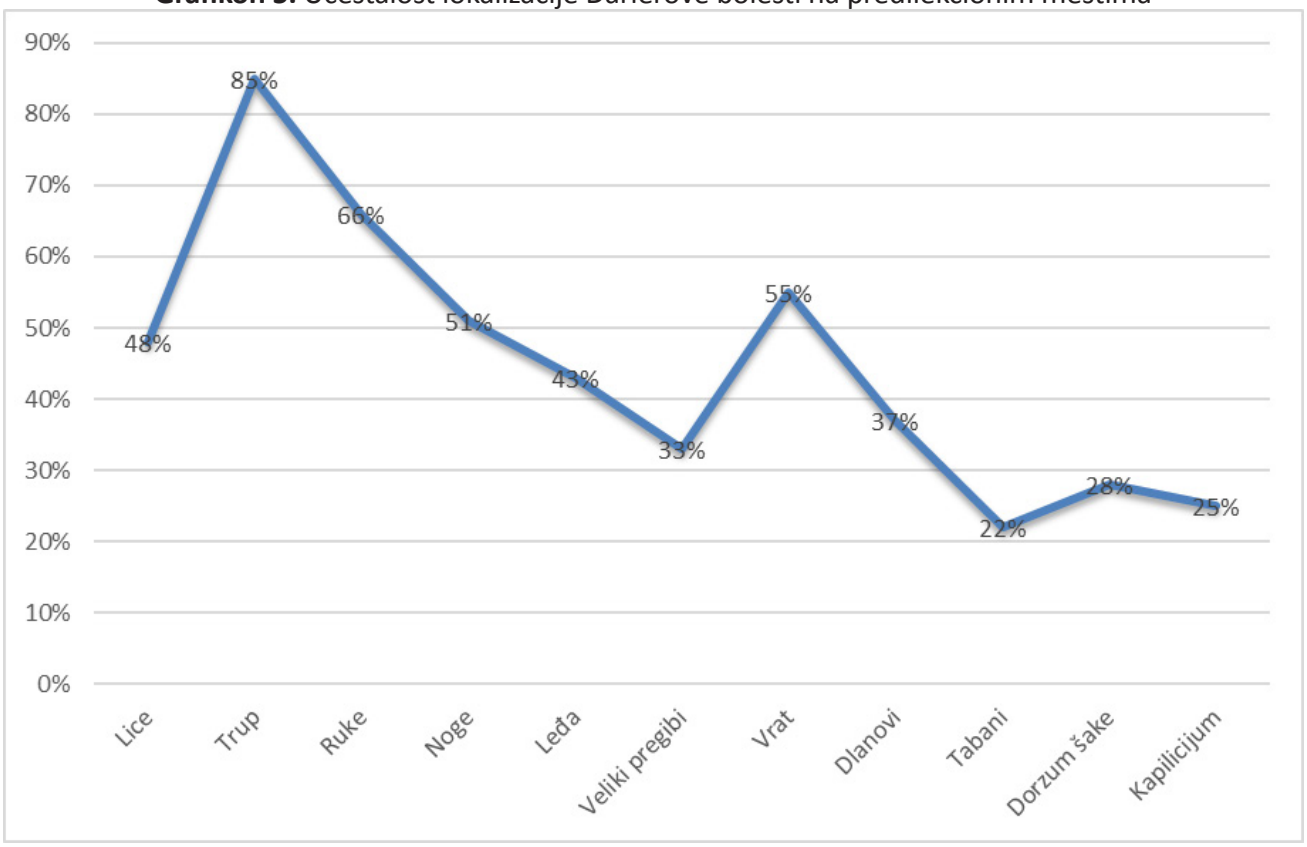
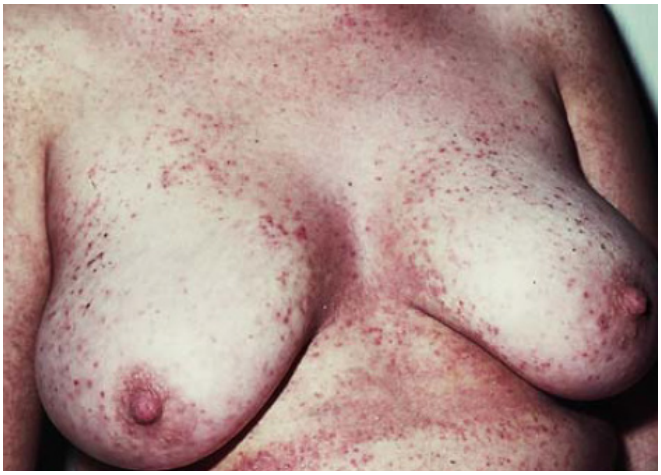


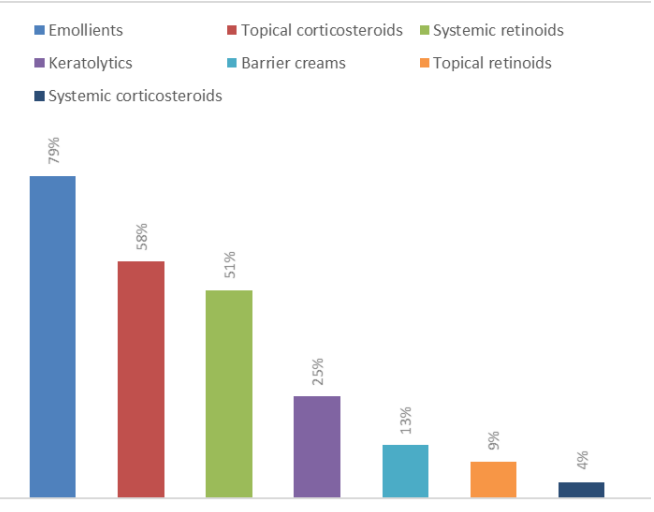
Figure 1. Characteristic hyperkeratotic papules in a typical distribution (presternal and submammary regions) in a patient with Darier disease



The analysis of the localization of lesions showed a predominant involvement of seborrheic regions, primarily the trunk, neck and extremities (Figure 5). Neuropsychiatric comorbidities were observed in 16% of patients.

Topical therapy was used in all patients, most frequently in the form of emollients (79%) and local corticosteroids (58%). Systemic retinoids were administered in 51% of patients, predominantly in generalized and clinically more pronounced forms of the disease (Figure 6).

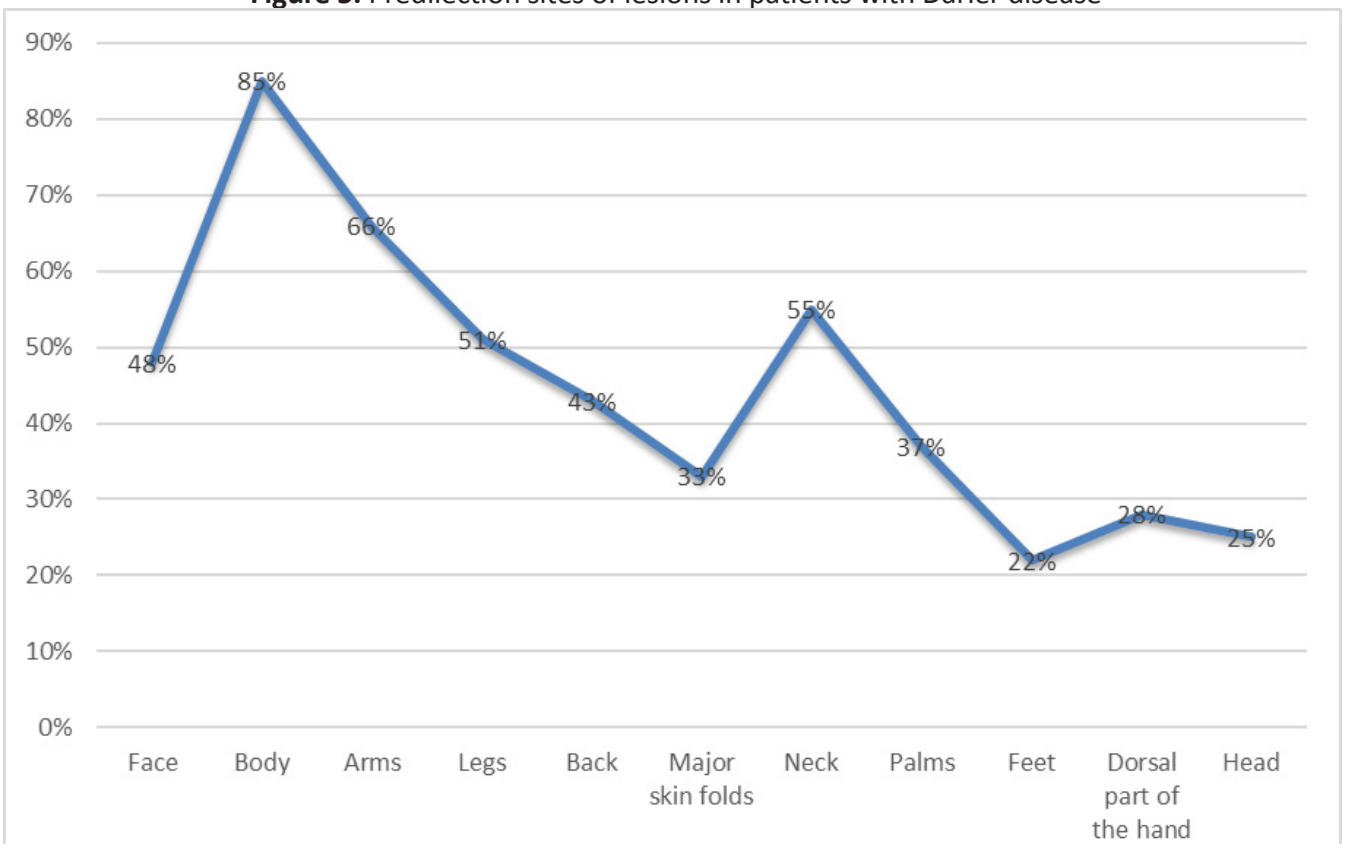
Figure 6. Therapeutic modalities in patients with Darier disease



Discussion

The results of the retrospective case series confirm that *Morbus Darier* most commonly appears during adolescence and early adulthood, which is consistent with clinical descriptions from contemporary literature reviews. Takagi et al. (1) state that the first lesions in most cases appear during the second decade of life, while Ettinger et al. (3) confirm that the disease typically occurs in puberty, and is characterized by a chronic relapsing-remitting course. Our data, according to which 76% of patients first presented with lesions in the first three decades of life, are consistent with this pattern.

Figure 5. Predilection sites of lesions in patients with Darier disease



se 76% pacijenata prvi put javilo sa promenama u prve tri decenije života, uklapaju se u ovaj obrazac.

Polna distribucija u našoj seriji pokazala je blagu predominaciju ženskog pola. Međutim, većina preglednih radova ukazuje na približno jednaku zastupljenost oba pola (1,9). S obzirom na relativno mali uzorak i jednocentrični karakter studije, razlika u našoj populaciji verovatno odražava distribuciju upućenih pacijenata, a ne stvarnu epidemiološku razliku.

Genetska osnova bolesti danas je dobro definisana kroz mutacije gena *ATP2A2*, koji kodira SERCA2 pumpu i ima ključnu ulogu u regulaciji intracelularne homeostaze kalcijuma. Moschella i sar. (2) ističu da poremećaj kalcijumske signalizacije dovodi do gubitka dezmozomalne adhezije i abnormalne keratinizacije, što objašnjava histopatološki nalaz suprabazalne akantolize i diskeratoze. Iako u našoj seriji nije sprovođena molekularna analiza, prisustvo pozitivne porodične anamneze kod gotovo polovine pacijenata potvrđuje autozomno dominantni obrazac nasleđivanja.

Značajna fenotipska varijabilnost, uključujući intrafamilijarne razlike, dobro je dokumentovana. Onozuka i sar. (4) pokazali su da članovi iste porodice sa identičnom mutacijom mogu imati različitu kliničku ekspresiju. Ruiz-Perez i sar. (10) ukazali su da određene missense mutacije mogu biti povezane sa varijabilnim kožnim fenotipom, dok neuropsihijatrijske manifestacije nisu striktno vezane za tip mutacije. Identifikacija novih mutacija, uključujući sporadične slučajeve (11) i teške fenotipe povezane sa specifičnim mutacijama (12), dodatno potvrđuje genetsku heterogenost bolesti.

U našoj seriji slučajeva registrovana je učestalost neuropsihijatrijskih poremećaja od 16%. Ovaj nalaz je u skladu sa savremenim populacionim istraživanjima. Curman i sar. (6) pokazali su povećan rizik za neurodegenerativne poremećaje i epilepsiju kod pacijenata sa Darierovom bolešću, dok su ranije studije ukazivale na povezanost sa afektivnim i kognitivnim poremećajima (13). Ovi podaci sugerišu da Darierovu bolest ne treba posmatrati isključivo kao dermatološko oboljenje, već kao sistemsku bolest sa mogućim neurološkim implikacijama.

Pored neuropsihijatrijskih komorbiditeta, u literaturi su opisane i druge sistemske asocijacije. Bachar-Wikstrom i sar. (7) identifikovali su povećan rizik od srčane insuficijencije, dok su Ahanian i sar. (8) ukazali na specifičan metabolički fenotip povezan sa Darierovom bolešću. Iako u našoj studiji ove asocijacije nisu sistematski analizirane, one ukazuju na potrebu šire kliničke procene pacijenata. Terapijski pristup u našoj seriji oslanjao se na standardne mere. Lokalna terapija, uključujući emolijense i kortikosteroide, predstavlja osnovu lečenja (9). Sistemski retinoidi ostaju terapija izbora kod umerenih i teških formi bolesti, uz značajno poboljšanje kliničke slike, ali i mogućnost neželjenih efekata koji zahtevaju pažljivo praćenje (9). Takagi i sar. (1) takođe navode da retinoidi efikasno redukuju hiperkeratozu i inflamaciju, bez uticaja na osnovni genetski poremećaj.

Ettinger i sar. (3) naglašavaju da, uprkos napretku u razumevanju molekularne patogeneze, terapijske opcije i dalje ostaju ograničene i uglavnom simptomatske. U tom kontekstu, istraživanja ciljanih terapija usmerenih na regulaciju kalcijumske homeostaze predstavljaju potencijalni iskorak. Hunt i sar. (14) pokazali su da dantrolen može korigovati ćelijske poremećaje karakteristične za Darierovu bolest u eksperimentalnim modelima, dok je u pojedinačnim kliničkim izveštajima opisana uspešna primena naltreksona (15). Ipak, ove terapije su još uvek u fazi evaluacije i ne predstavljaju standardnu kliničku praksu.

Naši rezultati potvrđuju da je u kliničkoj praksi terapija i dalje usmerena na kontrolu relapsa i ublažavanje simptoma, uz zadovoljavajući terapijski odgovor kod većine pacijenata. Međutim, hroničan tok bolesti i povremene egzacerbacije ukazuju na potrebu razvoja ciljane terapije zasnovane na molekularnim mehanizmima bolesti.

Fenotipska varijabilnost, od blagih do diseminovanih formi, značajno utiče na kvalitet života i otežava standardizaciju terapijskog pristupa (5).

Ova studija ima određena ograničenja koja treba uzeti u obzir pri tumačenju rezultata. Retrospektivni dizajn i oslanjanje na medicinsku dokumentaciju podrazumevaju mogućnost nepotpunih podataka. Tokom petnaestogodišnjeg perioda dokumentacija nije bila potpuno standardizovana, što je ograničilo dostupnost pojedinih varijabli.

Iz navedenog razloga nije sprovedena inferencijalna statistička obrada. S obzirom na nepotpunost podataka, primena složenijih statističkih modela mogla bi dovesti do parcijalne analize i potencijalno pogrešnih zaključaka. Stoga je primenjen deskriptivni pristup, koji najverodostojnije prikazuje raspoložive podatke.

Studija je jednocentrična, što ograničava mogućnost generalizacije rezultata. Ipak, imajući u vidu

Sex distribution in our case series showed a slight female predominance. However, the majority of review articles indicate approximately equal distribution of both sexes (1,9). Given the relatively small sample and the single-center character of the study, the difference in our population probably reflects the distribution of referred patients, rather than a true epidemiological difference.

The genetic basis of the disease is today well defined through mutations in the ATP2A2 gene, which encodes the SERCA2 pump and plays a key role in the regulation of intracellular calcium homeostasis. Moschella et al (2) point out that the disruption in calcium signaling leads to the loss of desmosomal adhesion and abnormal keratinization, confirmed by the histopathological findings of suprabasal acantholysis and dyskeratosis. Although molecular analysis was not conducted in our case series, the presence of positive family history in almost half of patients confirms the autosomal dominant inheritance pattern.

Considerable variability in the disease phenotype, including intra-familial variability, is well documented. Onozuka et al. (4) showed that members of the same family with an identical mutation can have different clinical expression. Ruiz-Perez et al. (10) indicated that certain missence mutations may be associated with variant cutaneous phenotypes, while neuropsychiatric features are independent of mutation class. The identification of new mutations, including sporadic cases (11) and severe phenotypes associated with specific mutations (12), further confirms the genetic heterogeneity of the disease.

In our case series, the frequency of neuropsychiatric disorders of 16% was registered. This finding gains additional importance in the light of contemporary population studies. Curman et al. (6) showed an increased risk of neurodegenerative disorders and epilepsy in patients with Darier disease, while previous studies indicated an association with affective and cognitive disorders (13). These data suggest that Darier disease should not be observed solely as a dermatological disease, but as a systemic disease with possible neurological implications.

In addition to neuropsychiatric comorbidities, other systemic associations have been described in the literature. Bachar-Wikstrom et al. (7) identified an increased risk of heart failure in the population with Darier disease, whereas Ahanian et al. (8) pointed to the specific metabolic phenotype associated with the disease. Although these associations were not systematically analyzed in our study, the above mentioned data indicated the need for a broader clinical assessment of patients. The therapeutic approach in our case series relied on standard measures that are recommended in the literature. Topical therapy, including emollients and corticosteroids, is the mainstay of treatment (9). Haber and Dib (9) point out that systemic retinoids remain the therapy of choice in moderate and severe forms of the disease with a significant improvement in the clinical presentation, but also with potential side effects that require careful monitoring. Takagi et al. (1) also report that retinoids effectively reduce hyperkeratosis and inflammation, but do not affect the underlying genetic disorder.

In a contemporary review by Ettinger et al. (3), it is emphasized that despite advances made in the understanding of molecular pathogenesis, therapeutic options still remain limited and mostly symptomatic. In this context, research into new therapeutic approaches aimed at regulating calcium homeostasis represents a significant step forward. Hunt et al. (14) showed that dantrolene can correct cellular disease features of Darier disease in experimental models, while in individual clinical reports, the successful administration of naltrexone was described (15). However, these therapies are still in the evaluation phase and do not represent standard clinical practice.

Our results confirm that in real clinical conditions, therapy is still aimed at relapse control and symptom relief, with a satisfactory therapeutic response in most patients. However, the chronic cause of disease and occasional exacerbations indicate the need for further research into targeted therapies based on the molecular mechanisms of the disease.

Considerable variability in the disease phenotype described in clinical case reports confirms that the clinical spectrum of the disease can be diverse, from mild forms to pronounced, disseminated lesions that significantly affect the quality of life. This variability further complicates the standardization of the therapeutic approach (5).

This study has certain limitations that should be considered when interpreting the results. The study is retrospective and based on the analysis of medical records, which implies that it depends on the quality and completeness of existing data. During the observed period of fifteen years, the documentation was not completely standardized, and therefore, certain clinical and therapeutic parameters were not available for all patients.

Due to this, a more detailed inferential statistical analysis was not carried out. Given that the database did not contain complete and uniform variables for all patients, the application of more complex statistical models could lead to partial analysis and potentially wrong conclusions. Therefore, a descriptive approach,

retkost oboljenja, prikazana serija predstavlja značajan doprinos razumevanju kliničko-epidemioloških karakteristika Darierove bolesti u praksi tercijarne zdravstvene zaštite.

Zaključak

Ova retrospektivna studija pruža sveobuhvatan prikaz epidemioloških i terapijskih karakteristika pacijenata sa Darierovom bolešću u uslovima tercijarne zdravstvene zaštite. Rezultati potvrđuju da se bolest najčešće manifestuje u adolescenciji i ranoj odrasloj dobi, sa izraženom fenotipskom varijabilnošću i značajnim udelom pozitivne porodične anamneze. Dominantna lokalizacija promena na trupu i potreba za kontinuiranom lokalnom terapijom u skladu su sa poznatim kliničkim obrascem bolesti. Uočen procenat neuropsihijatrijskih komorbiditeta dodatno naglašava potrebu za multidisciplinarnim pristupom u praćenju ovih pacijenata. Terapijski pristup je pretežno simptomatski, pri čemu sistemski retinoidi predstavljaju terapiju izbora kod težih formi. S obzirom na hroničan tok bolesti i ograničene kauzalne terapijske mogućnosti, buduća istraživanja trebalo bi da budu usmerena ka ciljanom delovanju na molekularne mehanizme bolest

Literatura

1. Takagi A, Kamijo M, Ikeda S. Darier disease. J Dermatol. 2016;43(3):275-279. doi:10.1111/1346-8138.13230
2. Moschella B, Busciglio S, Ambrosini E, Cesarini S, Caramanna L, Zanelli S, et al. Genetics of Darier's Disease: New Insights into Pathogenic Mechanisms. Genes (Basel). 2025;16(6):619. https://doi.org/10.3390/genes16060619
3. Ettinger M, Kimeswenger S, Deli I, Traxler J, Altrichter S, Noack P, et al. Darier disease: Current insights and challenges in pathogenesis and management. J Eur Acad Dermatol Venereol. 2025 May;39(5):942-951. doi: 10.1111/jdv.20448.
4. Onozuka T, Sawamura D, Yokota K, Shimizu H. Mutational analysis of the ATP2A2 gene in two Darier disease families with intrafamilial variability. Br J Dermatol. 2004;150(4):652-7. doi:10.1111/j.0007-0963.2004.05868.x.
5. Beiu C, Giurcaneanu C, Mihai M, Popa L, Hage R. Darier Disease - A Clinical Illustration of Its High Variable Expressivity. Cureus. 2019;11(12):e6292. Published 2019 Dec 4. doi:10.7759/cureus.6292
6. Curman P, Jebril W, Larsson H, Bachar-Wikstrom E, Cederlöf M, Wikstrom JD. Darier disease is associated with neurodegenerative disorders and epilepsy. Sci Rep. 2024;14(1):7109. doi: 10.1038/s41598-024-57779-4.
7. Bachar-Wikstrom E, Curman P, Ahanian T, Leong IUS, Larsson H, Cederlöf M, Wikstrom JD. Darier disease is associated with heart failure: a cross-sectional case-control and population based study. Sci Rep. 2020;10(1):6886. doi: 10.1038/s41598-020-63832-9.
8. Ahanian T, Curman P, Leong IUS, Brismar K, Bachar-Wikstrom E, Cederlöf M, Wikstrom JD. Metabolic phenotype in Darier disease: a cross-sectional clinical study. Diabetol Metab Syndr. 2020;12:12. doi: 10.1186/s13098-020-0520-0.
9. Haber RN, Dib NG. Management of Darier disease: A review of the literature and update. Indian J Dermatol Venereol Leprol. 2021;87(1):14-21. doi:10.25259/IJDVL_963_19
10. Ruiz-Perez VL, Carter SA, Healy E, Todd C, Rees JL, Steijlen PM, et al. ATP2A2 mutations in Darier's disease: variant cutaneous phenotypes are associated with missense mutations, but neuropsychiatric features are independent of mutation class. Hum Mol Genet. 1999 Sep;8(9):1621-30. doi: 10.1093/hmg/8.9.1621.
11. Liang YH, Zhang QG, Liu QX. Two novel missense mutations of ATP2A2 in two Chinese patients with sporadic Darier disease. Clin Exp Dermatol. 2015 Mar;40(2):201-3. doi: 10.1111/ced.12452.
12. Godic A, Glavac D, Korosec B, Miljković J, Potocnik M, Kansky A. P160L mutation in the Ca(2+) ATPase 2A domain in a patient with severe Darier disease. Dermatology. 2004;209(2):142-4. doi: 10.1159/000079600.
13. Jacobsen NJ, Lyons I, Hoogendoorn B, Burge S, Kwok PY, O'Donovan MC, Craddock N, Owen MJ. ATP2A2 mutations in Darier's disease and their relationship to neuropsychiatric phenotypes. Hum Mol Genet. 1999 Sep;8(9):1631-6. doi: 10.1093/hmg/8.9.1631.
14. Hunt M, Wang N, Pupinyo N, Curman P, Torres M, Jebril W, Chatzinikolaou M, Lorent J, Silberberg G, Bansal R, Burner T, Zhou J, Kimeswenger S, Hoetzenecker W, Choate K, Bachar-Wikstrom E, Wikstrom JD. Dantrolene corrects cellular disease features of Darier disease and may be a novel treatment. EMBO Mol Med. 2024 Sep;16(9):1986-2001. doi: 10.1038/s44321-024-00104-3.
15. Smith-Pellegrin DL, Rivera-Vega M, Cazarín-Barrientos JR, Melgarejo-Gómez A, Messina-Baas OM, Cuevas-Covarrubias S. Naltrexone, a therapeutic alternative in Darier disease. Rev Med Hosp Gen Méx. 2021;84(4):177-80. doi:10.24875/hgmx.21000039

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which shows the available data most faithfully, was applied.

In addition, the study is a single-center study, which may limit the possibility of generalization of results. However, taking into consideration the rarity of this disease, the presented series represents a significant contribution to the understanding of clinical and epidemiological characteristics of *Morbus Darier* in the practice of the tertiary healthcare center.

Conclusion

This retrospective study provides a comprehensive review of epidemiological and therapeutic characteristics of patients with *Morbus Darier* at the tertiary healthcare center. The results confirm that the disease most commonly appears in adolescence and early adulthood with pronounced variability in the disease phenotype and a significant share of positive family history. The predominant localization of lesions on the trunk and the need for continuous topical therapy are consistent with the known clinical pattern of the disease. The observed percentage of neuropsychiatric comorbidities further emphasizes the need for a multidisciplinary approach in the follow-up of these patients. The therapeutic approach is predominantly symptomatic, with systemic retinoids being the treatment of choice for more severe forms. Considering the chronic course of the disease and the limited causal therapeutic possibilities, future research should be directed towards targeting the molecular mechanisms of the disease.

References

1. Takagi A, Kamijo M, Ikeda S. Darier disease. J Dermatol. 2016;43(3):275-279. doi:10.1111/1346-8138.13230
2. Moschella B, Busciglio S, Ambrosini E, Cesarini S, Caramanna L, Zanelli S, et al. Genetics of Darier's Disease: New Insights into Pathogenic Mechanisms. Genes (Basel). 2025;16(6):619. https://doi.org/10.3390/genes16060619
3. Ettinger M, Kimeswenger S, Deli I, Traxler J, Altrichter S, Noack P, et al. Darier disease: Current insights and challenges in pathogenesis and management. J Eur Acad Dermatol Venereol. 2025 May;39(5):942-951. doi: 10.1111/jdv.20448.
4. Onozuka T, Sawamura D, Yokota K, Shimizu H. Mutational analysis of the ATP2A2 gene in two Darier disease families with intrafamilial variability. Br J Dermatol. 2004;150(4):652-7. doi:10.1111/j.0007-0963.2004.05868.x.
5. Beiu C, Giurcaneanu C, Mihai M, Popa L, Hage R. Darier Disease - A Clinical Illustration of Its High Variable Expressivity. Cureus. 2019;11(12):e6292. Published 2019 Dec 4. doi:10.7759/cureus.6292
6. Curman P, Jebril W, Larsson H, Bachar-Wikstrom E, Cederlöf M, Wikstrom JD. Darier disease is associated with neurodegenerative disorders and epilepsy. Sci Rep. 2024;14(1):7109. doi: 10.1038/s41598-024-57779-4.
7. Bachar-Wikstrom E, Curman P, Ahanian T, Leong IUS, Larsson H, Cederlöf M, Wikstrom JD. Darier disease is associated with heart failure: a cross-sectional case-control and population based study. Sci Rep. 2020;10(1):6886. doi: 10.1038/s41598-020-63832-9.
8. Ahanian T, Curman P, Leong IUS, Brismar K, Bachar-Wikstrom E, Cederlöf M, Wikstrom JD. Metabolic phenotype in Darier disease: a cross-sectional clinical study. Diabetol Metab Syndr. 2020;12:12. doi: 10.1186/s13098-020-0520-0.
9. Haber RN, Dib NG. Management of Darier disease: A review of the literature and update. Indian J Dermatol Venereol Leprol. 2021;87(1):14-21. doi:10.25259/IJDVL_963_19
10. Ruiz-Perez VL, Carter SA, Healy E, Todd C, Rees JL, Steijlen PM, et al. ATP2A2 mutations in Darier's disease: variant cutaneous phenotypes are associated with missense mutations, but neuropsychiatric features are independent of mutation class. Hum Mol Genet. 1999 Sep;8(9):1621-30. doi: 10.1093/hmg/8.9.1621.
11. Liang YH, Zhang QG, Liu QX. Two novel missense mutations of ATP2A2 in two Chinese patients with sporadic Darier disease. Clin Exp Dermatol. 2015 Mar;40(2):201-3. doi: 10.1111/ced.12452.
12. Godic A, Glavac D, Korosec B, Miljković J, Potocnik M, Kansky A. P160L mutation in the Ca(2+) ATPase 2A domain in a patient with severe Darier disease. Dermatology. 2004;209(2):142-4. doi: 10.1159/000079600.
13. Jacobsen NJ, Lyons I, Hoogendoorn B, Burge S, Kwok PY, O'Donovan MC, Craddock N, Owen MJ. ATP2A2 mutations in Darier's disease and their relationship to neuropsychiatric phenotypes. Hum Mol Genet. 1999 Sep;8(9):1631-6. doi: 10.1093/hmg/8.9.1631.
14. Hunt M, Wang N, Pupinyo N, Curman P, Torres M, Jebril W, Chatzinikolaou M, Lorent J, Silberberg G, Bansal R, Burner T, Zhou J, Kimeswenger S, Hoetzenecker W, Choate K, Bachar-Wikstrom E, Wikstrom JD. Dantrolene corrects cellular disease features of Darier disease and may be a novel treatment. EMBO Mol Med. 2024 Sep;16(9):1986-2001. doi: 10.1038/s44321-024-00104-3.
15. Smith-Pellegrin DL, Rivera-Vega M, Cazarín-Barrientos JR, Melgarejo-Gómez A, Messina-Baas OM, Cuevas-Covarrubias S. Naltrexone, a therapeutic alternative in Darier disease. Rev Med Hosp Gen Méx. 2021;84(4):177-80. doi:10.24875/hgmx.21000039

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