Preimplantation Genetic Screening in Darier-White Disease: A Case Report

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Introduction

Darier-White disease or Darier disease, also known as keratosis follicularis, is a rare genodermatosis with many degrees of severity and clinical manifestations that extend beyond the limits of the skin. It is a genetic disorder with an autosomal dominant inheritance pattern, and it can be treated, but not cured, in patients who have this medical condition [1]. The disease onset is usually before the third decade of life, with complete penetrance in adults and variable expression [2]. The prevalence of this disorder in the population is 1:55,000-100,000 [3]. Since this is a recurrent and long-term pathology, it could cause considerable social prejudice [4]. This work aims to present a case report exploring the applicability of the resources of preimplantation genetic diagnosis along with assisted reproduction techniques to prevent the transmission of Darier-White disease to one's descendants.

Objective

Darier-White disease is a rare genodermatosis with many degrees of severity and clinical manifestations that extend beyond the limits of the skin. It is a genetic disorder with an autosomal dominant inheritance pattern that can be treated, but not cured. Our work aims to report unpublished aspects on genetics and clinical presentation of Darier-White disease in Brazil, presenting a new genetic variant found in a female patient that has not been described so far. We also demonstrated the efficacy of the preimplantation genetic diagnosis along with techniques in assisted reproduction to with hold the occurrence of the Darier-White disease in future generations.

Methods

Case Report

Case Report

We hereby state that all Bioethics guidelines have been followed in this case report, and the patient has signed the Informed Consent Form. The patient is a 34-year-old female, white, married, a dental surgeon by profession; she was born in Rio de Janeiro, Brazil. She reports that the first onset of the condition was when she was nine years old, when xerosis was observed along with darkness of the neck and trunk, especially after exposure to sunlight. Later, a proliferation of scabs was seen in some seborrheic areas. At the same time, the onset of nail fragility was observed, with brittle nails. She denied systemic Preimplantation Genetic Screening in Darier-White Disease: A Case Report Archives of Dermatology and Skin Care V3 . I1 . 2020 3 complaints and was subjected to many topical treatments with little improvement.

A biopsy was conducted near the jaw angle. The histopathological exam showed hyperkeratotic epidermis, parakeratosis columns, granular aspect of the corneal layer, rounded bodies, predominantly suprabasilar acantholytic cleft, and the presence of perivascular lymphocytes in the superior reticular dermis. The patient currently shows an 80% improvement of the lesions with the use of oral acitretin combined with topical corticotherapy, with rotationof the acitretin use periods, mainly to preserve liver function. Occasionally, in disease relapse periods, mainly in the summer, the patient develops bacterial infections that are managed with the use of oral antibiotic therapy and hygiene of the infected lesion sites. In the disease history, she denied any comorbidities and identified similar conditions running in the family, including maternal grandfather, mother (Figure 4), aunt, and later, a cousin. The genogram of the family studies is shown in Figure 5. The first notice of the genetic disorder in the family history is Patient 0. This person has transmitted the pathology to two of his three daughters, propagating the disease through to the subsequent generations. The dominance previously described in the literature was identified, and the healthy children of a couple in which one of them has the disease did not transmit the pathology to the next generation. No specific cause for the onset of the disease was identified. As the patient wanted to get pregnant without transmitting the disease to her descendants, her ATP2A2 gene was fully sequenced for Darier-White disease. The patient's peripheral blood was collected in EDTA tubes and sent to theIgenomix® laboratory to extract genomic DNA, prepare DNA libraries and conduct the NGS-based sequencing. Clinical interpretation based on comparative data analysis using HGMD® Professional, Online Mendelian Inheritance in Man® (OMIM®), Publimed and other databases identified anundescribed splicing variant in heterozygosis, identified as NM170665.3:_c.2607+1_2607+2insT and classified as a variant of unknown significance (VOUS). To find out whether this variant is also causing DarierWhite disease together with the other variants as already described in medical literature, a segregation PCR study of the patient's family members, both affected and healthy, was subsequently conducted by the same laboratory using the peripheral blood samples of relatives of the patient, as follows: mother, maternal aunt, and maternal cousin, all presenting the same symptomatology for Darier-White disease

Results

Eleven ova were collected from the Darier-White disease patient, fertilized, and divided into four cycles over three years.
On 12 July 2019, in São Paulo, Brazil, the patient gave birth to a healthy baby boy who does not have the disease.

End

Darier-White disease is a serious genetic disease with an autosomal dominant inheritance pattern, complete penetrance, and variable expressivity in adults, appearing in different degrees of severity, which could cause considerable physical, mental, and social prejudice. The transmission of this monogenic disease to future generations can be hampered with PGD, PGS, and assisted reproduction. Combined with a genogram, these techniques enabled us to track a new genetic mutation causative of Darier-White disease and select healthy embryos to ensure that the mutated cell lineage could be controlled in this family, and prevented in their subsequent offspring. One of the significant advances of personalized medicine is the possibility of avoiding incurable diseases, which has successfully been achieved in this case.

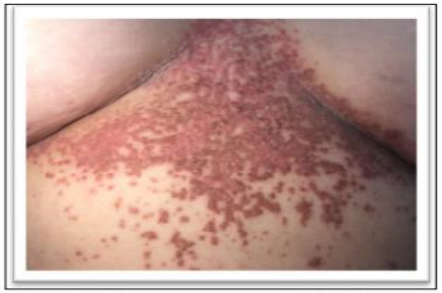

Figure 1. *Inframammary region of the female patient with Darier-White disease.*

Figure 2. *Scaly lesion in the scalp of the female patient with Darier-White disease.*

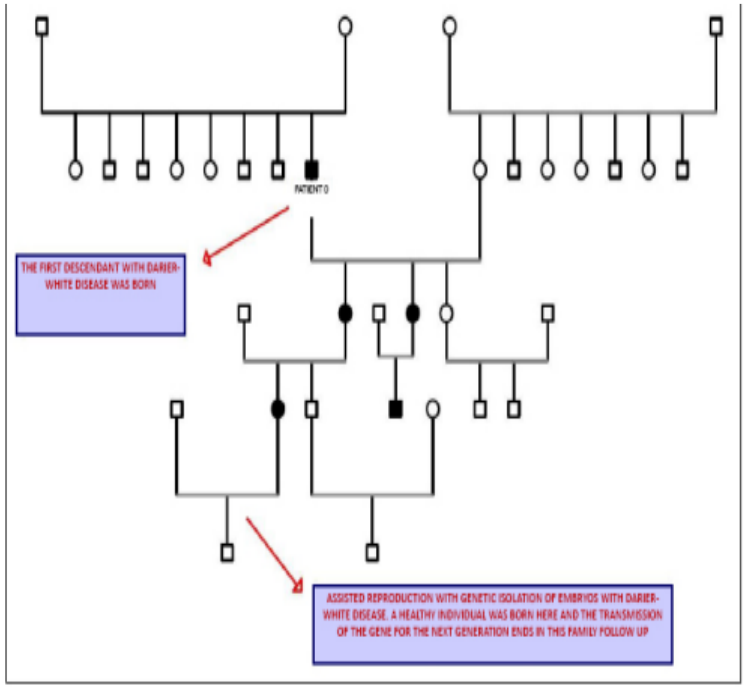

Figure 5. *Genogram illustrating the onset and progression of the Darier-White within the same family through five generations. It shows the onset from Patient 0 until the disease withhold with isolation of the embryos through preimplantation genetic screening and subsequent assisted reproduction.*

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