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Review Article

Vitiligo in Children: A Better Understanding of the Disease

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Abstract

Vitiligo is an important skin disease of childhood. The authors briefly discuss the etiopathobiology, clinics and comorbidities of the disease.

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Introduction

Vitiligo is an acquired, chronic, pigmentary disorder characterized by the progressive loss of cutaneous melanocytes and abnormality in their normal function, resulting in hypopigmented skin areas which progressively become amelanotic [1].

Different studies underline how half of vitiligo patients develop the disease before the age of 20 years old and how about 25% of them develop the disease before the age of 8 [2].

In pediatric age, vitiligo may represent a deep psychological trauma for both patients and their parents, and leads to a poor quality of life [3]. Even if the treatment of the disease is mail goal for dermatologists, a better understanding of vitiligo may be helpful for a better management of the patient.

Etiology

As well-known, vitiligo is inherited in a non-Mendelian, multifactorial and polygenic pattern.

A part for gene encoding molecules relevant for the normal melanogenesis (e.g. TYR which encode for Tyrosinase), recent studies show a strong association of vitiligo with particular HLA haplotypes (HLAs-A2, -DR4, -DR7, and –DQB1*0303) and other genes (Tab. 1) which are implicated in both cellular and humoral immunity [4][5][6]. Because the possible

associated to different autoimmune diseases, in future, the recognition of the genetic background should be helpful to recognize eventual comorbidities and personalized focused treatment.

Table 1: some of gene which may be alterated in vitiligo patients

Gene	Protein	Function	Comorbilities
RERE	Atrophin like protein 1	Regulation apoptosis	
PTPN22	Lymphoid specific protein tyrosinase phosphatase nonreceptor 22	Regulation T cell receptor signaling	Type 1 DM, Grave's disease, RA, Addison's disease, psoriasis, IBD
CTLA4B	Cytotoxic T lymphocytes antigen 4	Inhibition of T cells	Type 1 DM, Grave's disease, Hashimoto's thyroiditis, IBD, SLE
FOXP1	Forkhead box P1	Regulation of lymphoid cell development	
TSLP	Thymic stromal lymphoprotein	Regulation of T cell and DC maturation	
CCR6	Chemokine receptor type 6	Regulation of B cell differentiation	IBD, AR, Grave's disease
IL2RA	Interleukin 2 receptor	Regulation of lymphocyte response to bacteria	Type 1 DM, Grave's disease, RA, multiple sclerosis, SLE
GZMB	Granzyme B	Mediator of T cell and NK apoptosis	
FOXP3	Forkhead box P3	Regulation of T-reg	

Environmental factors

Many data support the deep impact of environmental factors in the development of vitiligo. First at all, there is the evidence of a variable prevalence of the disease in different countries, which range from 0.1 to 2.0%.

Then there are the data about the incidence of the disease among familiarities. It has been estimated that most of the cases of vitiligo are sporadic and up to 20% of patients report an affected relative. Moreover, the incidence of concordance of vitiligo in monozygotic twins is only 23% [7].

Different environmental factors (Tab. 2) may trigger the disease: their recognition would be fundamental to limit the incidence and progression of the skin disease.

Table 2: Trigger factors which may be involved in vitiligo onset

Physical stress: major illness, surgical operations, accidents
Intercurrent infections and repeated antibiotic- intake
UVR and sunburns
Chemical factors: Thiols, Phenols, Catechols, Mercaptoamines, Quinones and their derivatives
Endocrine factors: pregnancy
Malnutrition: malnutritional habits, intake of preserved, stale, junk flood
Psycho-social insecurity/shocks

Pathobiology

Today the exact pathobiology of vitiligo is still unclear. Even if multiple theories have been proposed (Tab. 3), recent data support that vitiligo is a T-cell mediated autoimmune disease, triggered by oxidative stress [8]. In melanocytes, the progressive accumulation of reactive oxygen species (ROS) causes DNA damage, lipid and protein peroxidation. Many are the proteins altered, showing partial or complete loss of their functionality. In particular tyrosinase is found to be inhibited by the high concentrations of hydrogen peroxide [9]. Also keratinocytes are significantly altered by oxidative stress, leading to a deficit of their trophic support to melanocytes [10].

Table 3: Pathobiological theories for vitiligo

• Oxydative stress theory
• Autoimmune theory
• Neurohumoral theory
• Autocytotoxic theory
• Biochemical theory
• Melanocytorrhagy theory
• Theory of decreased melanocyte lifespan
• Inflammatory theory

Clinic of vitiligo

Classically, vitiligo is characterized by asymptomatic white macules, varying in form and size. Although it is more often localized on body folds, periorificial and sun-exposed areas, vitiligo may affect different part of the body, both cutaneous and mucosal. Occasionally, patients may show the damage of the hair follicles' melanocytes, which result in depigmentated hairs (also known as "leukotrichia"). Characteristic is the Koebner's phenomenon, consisting in the development of new lesions at sites of skin trauma.

Table 4: Clinical variant of vitiligo [11-12]

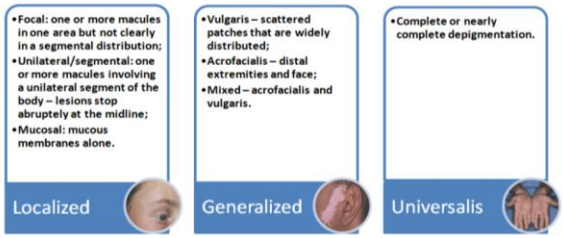
Type of vitiligo	Characteristics
Punctata vitiligo	little, punctuate-like, depigmented macules
Follicular vitiligo	vitiligo involving the follicular reservoir with poor cutaneous lesions
Inflammatory vitiligo	erythematous halo surrounding the white patches
Trichrome vitiligo	hypo-pigmented area between the central amelanotic zone and the peripheral normal skin
Quadrichrome vitiligo	variant of trichrome vitiligo with foci of repigmentation at the follicular osti
Pentachrome vitiligo	lesions show the occurrence of five shade of color, by white to black
Blue vitiligo	bluish appearance of skin color

In addition to such more common clinical features, vitiligo patients may also show abnormalities of the melanocytes localized in different districts (e.g. eyes, ears, brain, heart and lungs) [13].

Classification

Another classification of the skin disease, often preferred to the first one, is based on the clinical feature and natural history of vitiligo (Tab. 6) [14].

Table 5: classification of vitiligo on the basis of the disease distribution



Recognize the type of vitiligo has important implication for the management of the patient, because for each form there is a different prognosis (Tab. 7).

Table 6: Classification of vitiligo based on the clinical feature and natural history of the disease

Types	Characteristics	Subtypes
Segmental vitiligo (SV)	One or more vitiliginous patches, in a linear or flag-like pattern of mosaicism, with a unilateral dermatomal distribution	Unisegmental Bisegmental Multisegmental
Non-segmental vitligo (NSV)	Heterogeneous group of pigmentary disorders with different localization, usually in a symmetric pattern	Acrofacial Mucosal (more than 1 side affected) Generalized Universal Mixed (associated with segmental vitiligo) Rare forms
Unclassified or indeterminate		Focal Mucosal (only one side)

Comorbidities

The increased risk of developing autoimmune diseases of vitiligo patients is a well-known data (Tab. 8) [15].

Table 7: Prognosis of different forms of vitiligo

- Localized – stable, regressive
- Generalized – progressive, systemic, possible association with other autoimmune diseases
- Universalis – common association with comorbidities

Even if at the moment no laboratory biomarker are available to evaluate the possible association with autoimmune comorbidities, it is recommended to rule out the presence of associated diseases thought the commonest autoimmune antibodies and clinical laboratory data (Tab. 9).

Table 8: common autoimmune diseases associated to vitligo

- Alopecia areata
- Atopic dermatitis
- Autoimmune hemolytic anemia
- Autoimmune thyroid disease
- Diabetes mellitus
- Inflammatory bowel disease
- Morphea
- Multiple sclerosis
- Pemphigus vulgaris
- Pernicious anemia
- Psoriasis
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Others

Finally, even if more rare especially in childhood, recent studies underline the possible association of vitiligo with different diseases, such as endocrinologic ones (e.g. hypoparathyroidism) and systemic inflammatory disorders (e.g. obesity, metabolic syndrome) [16].

Table 9: Antibodies and laboratory data to be checked in a patient with vitiligo

Ab to be checked • Routine o Anti-thyroid peroxidase Ab (ATPO) o Anti-thyroglobulin Ab (ATG) o Anti-thyroid o Anti-parietal gastric cell antibody o Total IgE • Second line o Anti-nuclear Ab (ANA) o Additional autoantibodies (only if patient's history, family history and/or laboratory parameters highlight a strong risk of additional autoimmune disease or if endocrinologist /immunologist advice if multiple autoimmune syndrome detected
Laboratory data • Thyroid stimulating hormone (TSH) • Eosinophil count • Vitamin B12 • Folic acid

In conclusion, vitiligo may be considered as a spectrum of diseases with different clinical presentations, unknown etiology, fragmented genetic data and pathobiological hypothesis. We strongly affirm the importance of a better knowledge of the etio-pathobiology and clinic of the disease, for a better management of the patients.

References

1. Hercogová J, Schwartz RA, Lotti TM. Classification of vitiligo: a challenging endeavor. Dermatol Ther. 2012; 25(Suppl 1):S10-6. https://doi.org/10.1111/dth.12010 PMid:23237033

2. Halder RM, Grimes PE, Cowan CA, et Al Childhood vitiligo. J Am Acad Dermatol. 1987; 16:948–54. https://doi.org/10.1016/S0190-9622(87)70119-4

3. Manzoni AP, Weber MB, Nagatomi AR et Al. Assessing depression and anxiety in the caregivers of pediatric patients with chronic skin disorders. An Bras Dermatol. 2013; 88(6):894-9. https://doi.org/10.1590/abd1806-4841.20131915 PMid:24474096 PMCid:PMC3900338

4. Lee BW, Schwartz RA, Hercogová J, Valle Y, Lotti TM. Vitiligo road map. Dermatol Ther. 2012; 25(Suppl 1):S44-56. https://doi.org/10.1111/dth.12006 PMid:23237038

5. Jin Y, Ferrara T, Gowan K, et al. Next-generation DNA re-sequencing identifies common variants of TYR and HLA-A that modulate the risk of generalized vitiligo via antigen presentation. J Invest Dermatol. 2012; 132(6):1730–1733. https://doi.org/10.1038/jid.2012.37 PMid:22402439 PMCid:PMC3513338

6. Zhang XJ, Chen JJ, Liu JB. The genetic concept of vitiligo. J Dermatol Sci. 2005; 39(3):137–146. 73.

7. Alkhateeb A, Fain PR, Thody A et Al. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families. Pigment Cell Res. 2003; 16:208-14. https://doi.org/10.1034/j.1600-0749.2003.00032.x PMid:12753387

8. Shah AA, Sinha AA. Oxidative stress and autoimmune skin disease. Eur J Dermatol. 2013; 23(1):5-13. PMid:23420016

9. Gianfaldoni S, Zanardelli M, Lotti T. New technology for Vitiligo repigmentation. Ceska dermato-venerologie. 2014; (4):39-41.

10. Prignano F, Pescitelli L, Becatti M, et al. Ultrastructural and functional alterations of mitochondria in perilesional vitiligo skin. J Dermatol Sci. 2009; 54:157–67. https://doi.org/10.1016/j.jdermsci.2009.02.004 PMid:19282153

11. Lee DY, Kim CR, Lee JH. Trichrome vitiligo in segmental type. Photodermatol Photoimmunol Photomed. 2011; 27(2):111-112. https://doi.org/10.1111/j.1600-0781.2011.00572.x PMid:21392115

12. Chandrashekar L. Dermatoscopy of blue vitiligo. Clin Exp Dermatol. 2009; 34(5):e125-126. https://doi.org/10.1111/j.1365-2230.2008.03155.x PMid:19438538

13. Huggins RH, Janusz CA, Schwartz RA. Vitiligo a sign of systemic disease. Indian J Dermatol Venereol Leprol. 2006; 72:68-71. https://doi.org/10.4103/0378-6323.19730 PMid:16481722

14. Ezzedine K, Lim HW, Suzuki T et Al. Revised classification/nomenclature of vitiligo and related issues: the Vitiligo Global Issues Consensus Conference. Pigment Cell Melanoma Res. 2012; 25(3): E1–13. https://doi.org/10.1111/j.1755-148X.2012.00997.x PMid:22417114 PMCid:PMC3511780

15. Lotti T, D'Erme AM. Vitiligo as a systemic disease. Clin Dermatol. 2014; 32(3):430-434. https://doi.org/10.1016/j.clindermatol.2013.11.011 PMid:24767192

16. Pietrzak A, Bartosińska J, Hercogová J et Al. Metabolic syndrome in vitiligo. Dermatol Ther. 2012; 25(Suppl 1):S41-43. https://doi.org/10.1111/dth.12012 PMid:23237037