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.

Introduction

Vitiligo is an acquired, chronic, pigmentation 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 association 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 altered in vitiligo patients

| Gene Name | Protein | Function | Comorbidities |
|-----------|---------|----------|---------------|
| FASLG    | Apoptosis | Regulation of apoptosis | Type 1 DM, Grave’s disease, RA, Addison’s disease, IBD |
| CXCL12  | Chemokine receptor type 6 | Chemokine receptor signaling | Type 1 DM, Grave’s disease, Hashimoto’s thyroids, IBD, SLE |
| FOXP3    | Forkhead box P3 | Regulation of T cell and NK cell differentiation | IBD, AR, Grave’s disease |
| SOCS3    | Suppressor of cytokine-induced signal | Inhibition of T cells | Type 1 DM, Grave’s disease, Hashimoto’s thyroids, IBD, SLE |

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 familiarity. 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

| Type of Trigger Factor | Characteristics |
|------------------------|-----------------|
| Physical stress | Major illness, surgical operations, accidents |
| Intercurrent infections | Repeated antibiotic intake |
| UV light | Sunburns |
| Chemical factors | Thioles, Phenols, Catechois, Quercocains, Quinones and their derivatives |
| Endocrine factors | Pregnancy |
| Malnutrition | Malnutilritional habits, intake of preserved, stale, junk food |
| Psycho-social insecurity | Injuries/shocks |

T-cell mediated autoimmun 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

- Oxidative stress theory
- Autoimmune theory
- Neurohumoral theory
- Autocytolitic theory
- Biomechanical theory
- Melanocyterithys 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 depigmented 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 |
|-----------------|-----------------|
| Punctate Vitiligo | Little, punctuate-like, depigmented macules |
| Folicular Vitiligo | Involving the follicular reservoir with poor cutaneous lesions |
| Inflammatory Vitiligo | Erythematous halo surrounding the white patches |
| Trichrome Vitiligo | Hypopigmented 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].

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

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

| Type                  | Characteristics                          | Subtypes                                      |
|-----------------------|------------------------------------------|-----------------------------------------------|
| Localized             | One or more vitiligenous patches, in a linear or flag-like pattern               | Acrofacial                                   |
| Generalized           | Bilateral or unilaterial, mosaicism      | Mucoal (more than 1 side affected)            |
| Universal             | Heterogeneous group of pigmentary disorders with different localization, usually in a symmetric pattern | Universal                                   |
|                       |                                         | Mixed (associated with segmental vitiligo)   |
| Unclassified or indeterminate |                                      | Focal or Mucoal (only one side)              |

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 8: common autoimmune diseases associated to vitiligo

- Alopecia areata
- Atopic dermatitis
- Autoimmune hemolytic anemia
- Autoimmune thyroid disease
- Diabetes mellitus
- Inflammatory bowel disease
- Morphea
- Multiple sclerosis
- Periphitis 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                                                        |
|------------------|----------------------------------------------------------------|
|                  | Anti-thyroid peroxidase Ab (ATPO)                               |
|                  | Anti-thyroglobulin Ab (ATG)                                    |
|                  | Anti-thyroid                                                    |
|                  | Anti-parietal gastric cell antibody                             |
|                  | Total IgE                                                       |
|                  | Second line                                                    |
|                  | Anti-nuclear Ab (ANA)                                          |
|                  | 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.

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
- Universal – 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).

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