

A Rare Case Report of Vitiligo Vulgaris in Pediatric Patient in Tertiary Care Hospital

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Abstract: Vitiligo is a disease that causes loss of skin colour in blotches .It can affect the skin or any part of body. It may also affect the hair, the inside of the mouth and even the eyes. There are a few major hypotheses for the pathogenesis of vitiligo. :1.Autoimmune pathogenesis is a longstanding and popular hypothesis.2.The neural hypothesis suggests that nerve endings release neurochemical substances that can decrease melanin production or damage melanocytes.3.The biochemical hypothesis implicates the accumulation of toxic intermediate metabolites of melanin synthesis and defective free radical defense and the buildup of excessive quantities of hydrogen peroxide (H2O2) as a cause for destruction of melanocytes. Other hypothesis include genetic factors ,defects in the structure and function of melanocytes, and deficiency in melanocyte growth factors are playing a role in the depigmentation process. Vitiligo can be triggered by stress to the melanin pigment producing cells of the skin ,melanocytes.The triggers which range from sunburn to mechanical trauma and chemical exposures, ultimately cause an autoimmune response that targets melanocytes,driving progressive skin depigmentation. Causes include Identifying cellular responses to stress including antioxidant pathways and the unfolded protein response, (UPR) as key players in disease onset. Characterizing immune responses that target melanocytes and drive disease progression. Identifying major susceptibility genes. Medical History plays a fundamental role in the diagnosis of Vitiligo Vulgaris.We present a Case Report of 4 years old male patient affected by Vitiligo Vulgaris and discuss its pathogenetic mechanism.

Keywords: Vitiligo vulgaris Melanin pigment producing cells of skin, Melanocytes, Genetic factors, Medical history, autoimmune pathogenesis.

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I. Introduction

Vitiligo is an acquired, chronic, pigmentary disorder characterized by the progressive loss of cutaneous melanocytes and abnormality in their normal function, resulting in hypo pigmented skin areas which progressively become a melanotic.

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 encodes for Tyrosinase.

A Recent studies show a strong association of vitiligo with particular HLA halo types (HLAS-A2,

-DR4, -DR7, -DQB1*0303) and other genes which are implicated in both cellular and humoral immunity.

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.

II. Case Report

A 4 years old male patient was referred to Pediatric Department ,Government General Hospital, Kurnool with the chief complaints of fever since 20 days, high grade ,Intermittent not associated with chills and rigors, not associated with rash ,temporarily relieved on taking medication. Based on Physical Examination He was Diagnosed as Vitiligo Vulgaris .His past medical history includes vitiligo vulgaris since 1year back and medications include Tacmod Ointment ,(0.03%) Monobenzene cream. Patient had been experiencing Burning sensation, itching on applying Tacmod Ointment. So he had stopped taking medication.

The patient reported the chief complaints of fever since 20 days, high grade, Intermittent, not associated with chills and rigors, rash, temporarily relieved on taking medication. He has cold and cough (Positive) since 2 days. He is diagnosed as Acute Respiratory Tract Infection and medications include Injection Ceftriaxone 500mg Iv, BD, Syrup. Paracetamol 4ml QID, ORS BD.

III. Etiology

Vitiligo is inherited in a non-mendelian, multifactorial and polygenic pattern. A Part for gene encoding molecules relevant for the melanogenesis.

E.g. : TYR which encode for Tyrosine.

A Recent studies show a strong association of vitiligo with particular HLA halotypes (HLA-A2, -DR4, -DR7, -DQB1*0303) and other genes which are implicated in both cellular and humoral immunity. Because the possible associated to different Autoimmune Diseases, in future the recognition of the genetic background should be helpful to recognize eventual comorbidities.

PATHOBIOLOGY

Vitiligo is a T-Cell mediated autoimmune disease, triggered by Oxidative stress. 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 Tyrosine is found to be inhibited by the high concentrations of Hydrogen Peroxide. Also Keratinocytes are significantly altered by Oxidative Stress, leading to a deficit of their trophic support to melanocytes.

PATHOBIOLOGICAL THEORIES FOR VITILIGO

1. Oxidative stress theory
2. Autoimmune theory
3. Neurohumoral theory
4. Autocytotoxic theory
5. Biochemical theory
6. Melanocytorrhagy theory
7. Theory of decreased melanocyte lifespan
8. Inflammatory theory.

OXIDATIVE STRESS THEORY

The oxidative stress theory of Vitiligo suggests that the main culprit in the pathogenesis of vitiligo is the intraepidermal accumulation of Reactive Oxygen Species (ROS), the most notorious of which is H₂O₂ whose concentration may reach up to one millimole.

At this concentration H₂O₂ leads to changes in the mitochondria and consequently apoptosis/death of the melanocytes.

Important markers of interest are Malondialdehyde (MDA), Selenium, Vitamins, Glutathione Peroxidase (GPX), Superoxide dismutase (SOD) and CAT.

MDA is a product of lipid peroxidation and an indicator of Oxidative stress.

Selenium is required for Glutathione Peroxidase (GPX) activity and is a major antioxidant present in the erythrocytes.

SOD scavenges Superoxide radicals and reduces their toxicity (converts O₂⁻ to O₂ and H₂O₂), and CAT converts H₂O₂ to O₂ and H₂O.

Significantly higher levels of SOD, decreased erythrocyte GPX activity, low levels of enzyme CAT and Vitamins C and E have been detected both in the epidermis and in the serum of Patients with Vitiligo.

AUTOIMMUNE AND CYTOTOXIC HYPOTHESIS

Aberration of immune surveillance results in melanocyte dysfunction or destruction.

The autoimmune theory proposes alteration in humoral and cellular immunity in the destruction of melanocytes of vitiligo.

The fact that nonsegmental vitiligo is more frequently associated with autoimmune conditions than is segmental vitiligo.

For these reason certain disorders have been linked to vitiligo such as Hashimoto Thyroiditis, Graves disease, Addison disease, Diabetes mellitus, Alopecia areata, Pernicious Anemia, Inflammatory bowel disease, Psoriasis and Autoimmune polyglandular Syndrome.

The most convincing evidence of an autoimmune pathogenesis is the presence of circulating antibodies against melanocyte proteins in patients with vitiligo.

In addition to Humoral immune mechanisms, strong evidence indicates involvement of cellular immunity.

Destruction of melanocytes may be directly mediated by auto reactive CD8 positive T cells.

Activated CD8positive T cells have been demonstrated in perilesional vitiligo.

CELLULAR IMMUNITY

The main culprits are CD8 positive cytotoxic T-cells in cellular immunity.

Perilesional skin biopsies have shown epidermotropic cutaneous lymphocytes antigen positive lymphocytes with an increased CD8+/CD4+ ratio, substantiating the role of cytotoxic T- cells in the pathogenesis of vitiligo.

These T- cells have been shown to bring about degenerative changes in the melanocytes and vacuolization of basal cells in the normal appearing perilesional skin in patients with actively spreading lesions.

An increased expression of CD25 and MHC 2(Specifically HLA –DR) and ability to secrete interferon gamma (IFN gamma) has been noted in these T-cells which lead to increased expression of intercellular adhesion molecule 1 and consequently increased T-cell migration to the skin leading to a vicious cycle.

High frequencies of Melan- A specific CD8Ppositive T cells have been found in patients with vitiligo and their number may correlate with disease extent.

HUMORAL IMMUNITY

Various subsets of antibodies are seen in patients with vitiligo and are categorized as those against cell surface pigment cell antigens, intracellular pigment cell antigens and non-pigment cell antigens.

Certain antigens namely VIT 40/75/90 named after their respective weights have been identified in around 83% patients with vitiligo.

Although VIT 90 is found exclusively on pigment cells, VIT40 and VIT 75 are considered common to both pigment and non pigment cells.

Non –specific antibodies against these antigens have been found in patients with vitiligo.

As melanocytes are much more sensitive to immune mediated injury, it is probable that minimal injury from non-specific antibodies may induce lethal harm to melanocytes, but not to the surrounding cells.

Antibodies against Tyrosinase and Tyrosinase related proteins 1 and 2 (TRP-1 and TRP-2), SOX 9 and SOX 10(TRANSCRIPTION FACTORS) involved in the differentiation of cells derived from the neural crest have also been detected in patients with autoimmune polyendocrine syndrome type 1 (APS1) and in patients with vitiligo without any concomitant disease.

AUTOCYTOTOXICITY

Toxic metabolites both intracellular such as those formed during melanin synthesis and extracellular such as phenols or quinines may accumulate and damage the melanocytes of genetically susceptible individuals bringing about autocytotoxic injury to the melanocytes.

It has been shown that TYROSINE upon entering the melaninogenic pathways produces certain electrically unstable by-products, which have the potential to damage other cellular substrates resulting in death of the melanocytes.

MELANOCYTORRHAGY

Theory of melanocytorrhagy proposes that NSV is a primary melanocytorrhagic disorder with altered melanocyte responses to friction which induces their detachment, apoptosis and subsequent transepidermal loss.

This theory adequately explains the koebners phenomenon because it proposes that weakly anchored melanocytes upon facing minor friction and or other stress undergo separation from the basement membrane migrate upward across the epidermis and are eventually lost to the environment resulting in vitiligo at the sites of trauma.

Patients with unstable vitiligo, the dendrites of perilesional melanocytes were small clubbed and retracted which were unable to adhere melanocytes to the basement membrane and the surrounding keratinocytes thereby rendering them more prone to transepidermal loss.

Tenascin an extracellular matrix molecule that inhibits the adhesion of melanocytes to fibronectin , has been found to be elevated in vitiliginous skin contributing to the loss of melanocytes or ineffective repopulation.

This results in focal gaps and impaired formation of basement membrane resulting in weakening of the basal attachment of melanocytes and subsequent chronic melanocyte loss known as Melanocytorrhagy. During transepidermal migration, damaged melanocytes could induce an immune response thereby perpetuating vitiligo.

GENETICS

Familial clustering is seen in vitiligo.

Vitiligo is a polygenic disease ,several candidate genes including Major Histocompatibility Complex (MHC), Angiotensin converting enzyme (ACE), Catalase (CAT), Cytotoxic –T Lymphocyte Antigen-4 (CTLA-4), Catechol –o-methyl transferase (COMT), Estrogen receptor (ESR), mannin-binding lectin (MBL2),

Protein Tyrosine Phosphatase, non-receptor type -22(PTPN22), Human leukocyte antigen(HLA),NACHT,Leucine-rich repeat protein (NALP1), X-box binding protein (XBP1), forkhead box p1 (FOXP1) and Interleukin -2 receptor A (IL-2RA), that are involved in the regulation of immunity have been tested for genetic association with generalized linkage.

Genome –wide linkage analysis has revealed autoimmune susceptibility (AIS) loci associated with vitiligo.

AIS1 was discovered to be located on chromosome 1p 31.3- p 32.2, AIS2 on chromosome 7 and AIS3 on chromosome 8.

AIS1 and AIS2 linkages were found to occur in families with vitiligo along with other autoimmune diseases, while AIS3 was found in the non- autoimmune family subgroup.

Another gene that is Systemic Lupus Erythematosus Vitiligo –related gene (SLEV1) located on chromosome 17, was found to be associated with generalized vitiligo present in association with other concomitant autoimmune diseases.

VITAMIN D DEFICIENCY

Low vitamin D serum levels have been associated with many autoimmune disorders and several other skin diseases.

Vitiligo is an autoimmune disease characterized by destruction of melanocytes by immune mechanisms.

Melanocytes express vitamin D receptors and their function can be affected by vitamin d status.

It is characterized by skin depigmentation as a result of destruction of melanocytes in the affected areas.

Vitamin D has a significant role in immunity (INNATE AND ADAPTIVE), Calcium regulation and melanin synthesis in addition many diseases have been associated with reduced vitamin D levels.

Melanocytes express receptors for vitamin D which may indicate a possible role for vitamin D in regulation of melanocyte function.



Figure 1: Segmental vitiligo involving Left Leg and forehead.

IV. Treatment

1. TOPICAL TREATMENTS:

(A) TOPICAL CORTICOSTEROIDS:-

The efficacy of topical corticosteroids in the treatment of vitiligo especially of localized forms on the face and other body's area is well known.

Steroids acts as anti-inflammatory and immunosuppressant agents (e.g.: Betamethasone dipropionate 0.05%, Clobetasol propionate ointment are usually preferred for the treatment of young patients.

The drugs may be applied once or twice a day in consecutive or alternative days.

(B) TOPICAL CALCINEURIN INHIBITORS:-

Topical calcineurin inhibitors (Tacrolimus and pimecrolimus) are considered valid alternatives to topical corticosteroids for the treatment of localized forms of vitiligo.

They act as immunomodulator agents by blocking calcineurin they inhibit the cytokines expression.

As topical corticosteroids, topical calcineurin inhibitors are indicated for the treatment of localized forms of vitiligo, also for the facial lesions where they seem to be safer than steroids.

Usually Topical Calcineurin Inhibitors are prescribed twice a day.

CALCIPOTRIOL

Calcipotriol is a synthetic Vitamin D3 Analogue.

It stimulates melanogenesis and to halt the melanocytes destruction by T-Cells.

It is applied once a day. It seems to be less effective than topical corticosteroids.

The treated sites should not be exposed to phototherapy to avoid cutaneous hypo pigmentation.

2. SYSTEMIC TREATMENT

(A) SYSTEMIC CORTICOSTEROIDS:

The systemic administration of corticosteroids (e.g.:- Betamethasone, Methylprednisolone) , which seem to be useful to stop the progression of the disease and to induce repigmentation.

Recently an oral minipulse therapy has been proposed.

It consists of the morning intake of betamethasone (0.1 mg/kg body weight on two consecutive days in a week for 12 weeks.

After that, patients have to assume 1mg/ month for the following three months.

The clinical results seem to be good.

3. PHOTOTHERAPIES

Ultraviolet radiations (UVR), both in the range of uvb and uva are considered as a first line therapy especially for extensive vitiligo, because of their good efficacy and tolerance.

The effects of UVR are both immunosuppression and stimulation of the melanocytes activity.

ORAL PUVA

TOPICAL CREAM PUVA

BATH PUVA

PUVA SOL

NARROW –BAND UVB.

PUVA THERAPY

PUVA THERAPY consists of the oral intake of a photosensitizing psoralen (8-methoxypsoralen, 5-methoxypsoralen or 4,5, 8- trimethylpsoralen) followed by exposure to photo activating uva light (320-400 nm).

Treatment is performed 2-3 times a week, increasing the dose of uva on the base of patient's response.

PUVA THERAPY should not be performed in children <12 years because of psoralens toxicity (e.g.:- gastric and ocular damage.

TOPICAL PUVA

A Valid therapeutic option for children with vitiligo is the topical puva.

It consists of the application of 0.1-0.01 % 8 Methoxypsoralen in hydrophilic petrolatum or ethanol onto the vitiligo skin followed by exposure to uva – irradiated with a dose of 0.12-0.25 J/CM².

TOPICAL PUVA SOL

Similar treatment is the topical PUVA SOL; after the topical application of a psoralen cream, the patient will be exposed to sunlight.

BATH PUVA

Patients take a warm bath with 0.5-1.0 mg/l 8 - methoxypsoralen for 20 minutes before they are exposed to uva.

4. SURGICAL THERAPIES

Suction blister epidermal grafting

Mini punch grafts

Thin Thiersch grafts

Transplantation of epidermal cell suspension

Cultured melanocyte suspension

Cultured epidermis.

V. Conclusion

- The prevalence of vitiligo among children is high and is predominant earlier age of onset among patients with family history of vitiligo or autoimmune disorders.
- Vitiligo is the most common presentation with lower limbs being the most common site of involvement.
- Parents should be advised that the treatment is often long term and requires their adherence.
- Disease should be referred early to potentialize treatment outcomes.
- The adverse effects include Pruritus, Burning sensations are seen in patient, Patient has stopped taking Topical Tacrolimus Ointment.
- Patient should be advised Photo protection along with the use of Sunscreens.
- We would like to suggest regular monitoring of patients on Tacrolimus for the development of this side effect.
- Patients should be adequately counseled regarding Disease, Drugs, and Side effects before Therapy was given.

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