CONTINUING MEDICAL EDUCATION

ETIOPATHOGENESIS OF VITILIGO: ARE WE DEALING WITH AN ENVIRONMENTAL DISORDER?

PN Behl, A Agarval, G Srivastava

The increasing incidence of vitiligo in this part of the world (4.25%), prompted us to study 5000 fresh vitiligo patients. Several triggering factors were elicitable. Malnutrition and intake of junk food were very common in childhood vitiligo. Intercurrent infections as well as intake of antibotics were also significant, immediately preceding the development of depigmented patches in younger age group. Genetic predisposition was uncommon. Autoimmune disorders were infrequent and usually accompanied late onset vitiligo.

For management, vitiligo was classified into VI (active), V2 (quiescent) and V3 (improving) stages. The therapy administered varied in each stage. As a common denominator, all out efforts were made to eliminate possible trigger factors in individual cases throughout the period of treatment, and building the general health to prevent recurrence in future.

The study strongly points out that vitiligo is a multifactorial disorder. It can be effectively managed after each patient is individually assessed. Elimination of possible triggering factors may form the mainstay of vitiligo therapy along with controlled pharmacological intervention. The improvement of general resistance of body may bring spontaneous repigmentation.

Introduction

Vitiligo is regarded as a primary acquired idiopathic, depigmentation of the skin and/or mucous membranes. Although a benign cutaneous pigmentary aberration with no influence on physical and intellectual capability of the affected individual or on life span, yet it is a dreaded disease of the pigmented race.[1] It puts tremendous stress on the sufferer and adversely effects his capability and social life. In the developing countries like India, it is frequently confused with leprosy by a lay person.

The fact that at least one percent of the world population has vitiligo speaks boldly for its common occurrence.[2] More over, not so encouraging views expressed by eminent physicians[3] about its treatment disheartens the patient as well as the treating doctor. As little is known about its etiology-being an idiopathic disorder-its treatment regimens widely differ. Thus, the response, subsequent recurrences and damage to the skin are also quite unwarranted. We highly felt that there is always a definite etiology in each case-a group of triggering factors. Unless and until we eliminate these factors we cannot treat a vitiligo patient satisfactorily. Further, if any such triggering stimulus is eliminated, the activity of the disease should stop per se, and spontaneous repigmentation may start. Keeping these facts in mind, our Institute started a detailed clinico-etiologic study of fresh vitiligo patients, spread over the past decade.

Materials and Methods

Five thousand fresh vitiligo patients were included in this study. The parameters in history included age-at-

From the Skin Institute & School of Dermatology, New Delhi, India.
Address correspondence to :
Dr. P N Behl

onset, duration, preceding events, history of drug intake, diet, water consumed, geographic area of stay and its surroundings, family history, and systemic illnesses and infections. They were further examined clinically for general assessment of health and nutrition, any overt focus of infection, site of initial affection and its spread, and the affection of mucous membrane and hair. This was followed by routine blood and urine investigation and an immunoglobulin study. In large number of cases, serum elements (copper, molybdinum, manganese, zinc etc.) were also estimated. Stools were examined for ova and cyst of parasites.

The treatment was instituted in a systemic way. In the first stage, (VI stage) the above measures along with other conservative measures like phenylalanine, placental extract-topical or systemic (in insidiously spreading VI stage), and ACTH injections (in galloping VI stage), antistress herbal preparations and building up general health of the body will go a long way in its treatment. In stable (V2) stage when no new lesions are appearing, photochemotherapy with psoralens (Ammi majus) can be added. In repigmenting stage (V3) when there is no further pigmentation, surgical measures can be undertaken thus preventing the injudicious use of psoralens. It is equally important to identify the resistant areas which may not repigment even after prolonged use of psoralens, as well as patients with poor response. The findings were recorded on a specially-devised exhaustive proforma. The material thus gathered was assessed at the end of the study, and the results recorded under various heads.

Observations

Age and sex incidence : Of the 5000 patients, 1313 had an age-at-onset below 10 years, and another 708 between 11 and 20 years. There were 2720 males and 2280 females

Table I : Age incidence

Age group (years)	Number
0 -10	1313
11-15	708
16-25	1147
26-35	788
36-45	648
46 & above	396
Total:	5000

(Table I) :

Family history : A positive family history of vitiligo was elicitable in 434 (8.4%) patients. Of these, 243 (4.8%) belonged to first degree relations, while 148 and 43 to second and third degree relations respectively.

Suspected precipitating factors/events : Certain events/factors were found to be clearly preceded or associated with the onset of vitiligo. The most likely event was taken into consideration in every case, wherever such a history was available, to avoid duplication of triggering events. However, there was an overlap in cases with recurrent infections in 200 patients, who also had repeated courses of chemotherapy, as both were regarded significant precipitating events in them (Table II). Most of the cases (130 out of 151) with overt malnutrition also showed associated dull, thin, brown hair with stunted growth, several months/years prior to the onset of vitiligo. Emotional trauma, such as a death in the family, broken marriage, unemployment and other stresses like major operations preceded onset of vitiligo in 70 (3.50%) patients. Among recurrent infections, focal sepsis including chronic tonsillitis/dental sepsis and intestinal amoebiasis were prominent. Broad-spectrum antibiotics especially tetracyclines were found to be the often prescribed medicine for the throat sepsis. Some children, under 8-10 years of age even showed terramycin induced

discoloration of the teeth. Amongst topical chemical agents, application of adhesive bindi on the forehead (1.5%) and wearing of rubber foot wear (0.7%) were significant triggering factors.

Trace elemental analysis done in 147 patients of vitiligo is shown in Table III. Serum copper levels were significantly lower in active stage in 142 of them (96.59%).

Table II. Probable precipitating (triggering) factors/events

Factor (s)	Total
1) Nutritional/Diet, Digestive Upsets	2570(51.4%)
2) Recurrent Infections	1713(34.26%)
3) Drug/Antibiotic NSAID, Hypertensives	1163(23.26%)
4) Allergy & Auto Immunity	819(16.38%)
5) Emotional Stress	1023(20.46%)
6) Ecology/Industrial Area Proximity/Pollution	449(8.98%)
7) Endocrinal	94(1.885)

Equivocal results were seen in the case of zinc, manganese and selenium.

Serum IgE levels were done in 500 patients. Of them, 241

Table III. Elemental analysis on vitiligo patients

	Above normal	Normal	Below normal	Total Patients
Cu	1 (0.680%)	4(2.72%)	142 (96.59%)	147
Zn	27 (25%)	78(72.22%)	3 (2.777%)	108
Mn	37 (41.57%)	37(41.57%)	15 (16.85%)	89
Se	11 (12.35%)	6(74.15%)	12 (13.48%)	89
Ni	1 (14.28%)	6(85.71%)	-	7
Cr	2 (40%)	3(60%)	-	5
Mo	1 (20%)	4(80%)	-	5

had a raised IgE level. Majority of patients with raised IgE level had a level of over 500 iu/ml.

Clinical features

The patients were conventionally classified as vitiligo vulgaris, acrofacialis, zosteriformis or mucosae (Table IV). Involvement of mucous membrane alone was fairly uncommon (0.35%); however it accompanied other varieties in 110 (10.5%) patients. The variation in the morphology of developing, quiescent and healing lesions, at the time of presentation, were quite distinct, which prompted us to further classify every case as VI (active), V2 (quiescent) and V3 (improving), VI stage patients were still developing new lesions, and the individual lesions were showing activity, with ill-defined, advancing borders. V2 patients had developed no lesions for past few months and had well demarcated skin lesions with hyperpigmented borders. V3 patients had no lesions for the past many months or years, with skin lesions well-defined with

Table IV. Types of vitiligo

Types	Number	Percentage
(a) Acral, Acrofacial	2080	41.6%
(b) Zosteriformis	265	5.3%
(c) Vulgaris	2375	47.5%
(d) Mucosal	280	5.6%

Table V. Activity of the disease at the time of presentation

Stages	Number	Percentage
VI (active)	3355	67.1%
V2 (quiescent)	1212	24.04%
V3 (improving)	443	8.86%

variable amount of healing within the patch. (Table V).

Treatment administered :

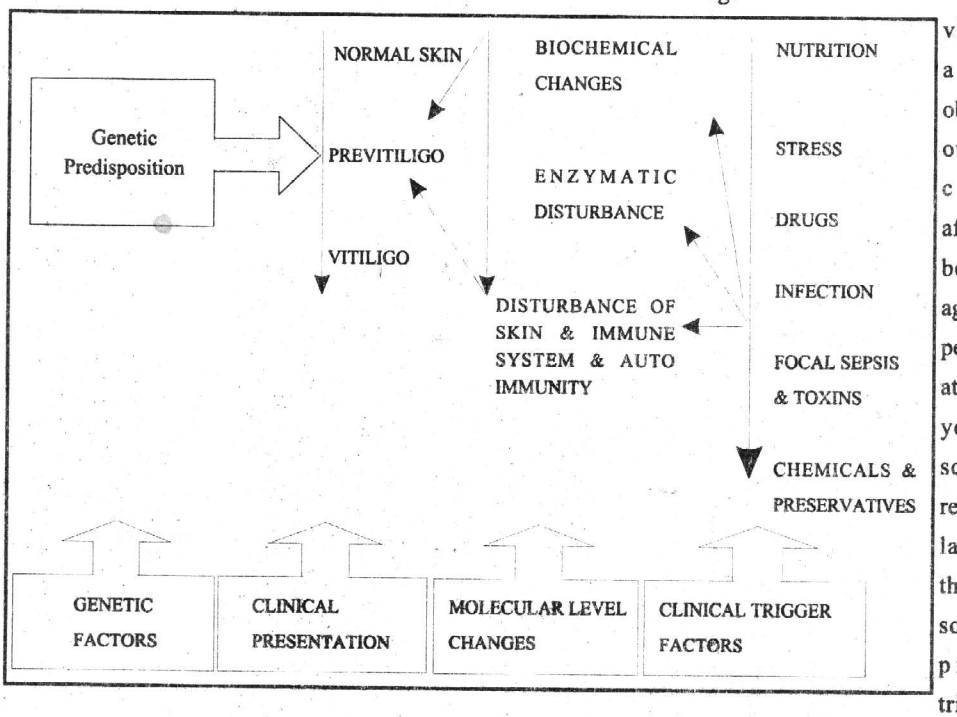
VI patients were given a conservative treatment along with elimination of the predisposing cause(s). V2 and V3 patients were given more active treatment, using psoralens to stimulate the melanocytes. However, V3 patients who appeared to have no further chance of repigmentation, were advised to undergo surgery.

Discussion

The possible etiological factors and their interactions is summarised in the following diagram

(Fig.1). Despite efforts to precisely pinpoint the exact cause of vitiligo, no breakthrough has been achieved. The present study has thus made another attempt to shed some light on the disease.

Table VI. Possible clinical causative factors in vitiligo



Various workers from all over the globe have found different incidences of vitiligo (Table VIII.) One salient feature appears to be that the incidence of vitiligo is on the rise especially in the developing countries like India. Over the past four decades, several camps have been conducted by us in the remote areas of India (Table VII). Certain areas in proximity to industries showed an alarming rise in incidence of vitiligo, possibly due to industrial wastes contaminating the ground water with vegetation grown in such water being consumed by natives. Correlation of number of patients of vitiligo with different age groups in childhood onset vitiligo showed a rise in the incidence of vitiligo as the age advanced (Fig.2). Certain experiments involving the feeding of guinea pigs on different water collected from various such industrial towns showed depigmentation of hair of these animals.

Much has been said about the age and sex incidence of vitiligo.[4-8] An alarming observation made in our study was the conspicuous affliction of children below 10 years of age. As much as 34.2 percent had the age-at-onset less than 10 years. On scrutinizing their records, we found a large number of these children had some or the other predisposing/ triggering factors- recurrent infections and/or antibiotic therapy, malnutrition and consumption of junk food having high contents of preservatives, colorants and anti-oxidants. Lerner,[4] observed that nearly 50 per cent of vitiligo developed below 20 years of age, while it was much higher (61.9%) in our series.

Vitiligo is believed to be a hereditary disorder probably inherited through an autosomal dominant gene of variable penetrance. The incidence of positive family history has variously been reported from 5% to 40% in different studies. In our study it was 21.7 per cent.In studies in two small communities in India, family history

was documented as high as 78.29%, and 90.38% respectively.[10,11] Vitiligo has been observed in monozygotic twins.[12]

Table VII. Incidence of vitiligo in various countries[24]

Author	Country	Incidence (%)
Africa		
El Mofty (1968)	Egypt	1.0
India		
Panja (1947)	Calcutta	6.0
Levai (1958)	Vellore	4.0
Punshi & Thakre (1969)	Amravathi	8.0
Behl and Bhatia (1972)	Delhi	8.8
Sehgal (1974)	Goa	2.9
Koranne and Sachdeva (1988) Delhi	1,23	
Baruah and Garg (1992) Pondichery	2.6	
Europe		
Howitz et al (1979)	Denmark	0.38
Grunnet et al (1970)	Denmark	1.44
Dawber (1968)	England	0.15
Dermons (1974)	France	3.0
Parrot et al (1973)	France	0.6
Fornara	Italy	0.3
Polotebrof	Russia	0.14
Robert (1941)	Switzerland	0.29
United States		
Canizers (1960)	Mexico	4.0
Ruiz Maldonado et al (1977) Medico	2.6	
Fitzpatrick et al (1974)	Massachusetts	8.0
Others		
Arakava	Japan	1.64
Ito (1952)	Sendan	1.3
Koch Oon Teik (1962)	Malaysia	0.7

The elucidation of precipitating factors in as many as 68.45 per cent patients in our study is quite significant. These were largely preventable, and require elimination for an effective cure. Although genetic, autoimmune, neurogenic and melanocyte self-destruction hypothesis have time and again been described[8,13] in the etiopathogenesis of vitiligo, the preceding factors have seldom been stressed. The occurrence of vitiligo after major illness, severe emotional stress, pregnancy, surgical operation and physical trauma has been recorded.[2,4,8] Some noxious, melanocyte-destroying chemical entering the body through diet, consumption of ready made preserved stale food/medicines/contaminated water (through industrial waste) or the air might be an important factor in precipitation of vitiligo in a susceptible host. The occurrence of vitiligo following repeated drug intake in as many as 535 (26.75 per cent) patients is far more than just a co-incidence, and warrants serious thought prior to prescribing antibiotic therapy in patients who have a family history of vitiligo. A high prevalence of vitiligo was noticed by the authors in the population near a textile industry. It did not have an effective waste disposal system and discharged the effluents in the nearby canal. These people used this contaminated water for drinking and irrigation purposes.

Table VIII. Incidence of vitiligo in India as seen in skin camps[24]

Place	Total No. of patients	Vitiligo patients	Percentage	Remarks
Rajkot	452	136	30.0	Industries
Dadua	300	20	7.0	Jungle area
Alwar	300	15	5.0	Township
Cphandousi	529	146	28.0	Carpet Industry
Naranaul	400	1	0.25	Farming
Rewari	800	8	1.0	No Industry
Khetri	320	1	0.3	Copper Mines
Philakwa	300	30	10.0	Industries

All these precipitating factors might have contributed to disturb the immunological balance of the body, thus causing an autoimmune or other process to paralyse the affected patient's melanocyte system to produce the lesions of vitiligo. Our presumption is further supported by the work of Puri et al[14] which suggests that in vitiligo whole of the melanocyte system is defective. It was also found that the cultured melanocytes were defective, stunted and slow growing. Further studies at the Skin Institute in histopathological sections of margins

of active vitiligo, showed the presence of mononuclear infiltrate hugging the basal layer of epidermis suggesting some type of auto-immune reaction.[25,26]

Management of the disease appeared to vary with the activity of the disease. Active or galloping vitiligo cases (VI-stage) required a different approach compared to the static and healing vitiligo (V2 and V3-stages). Every effort was made to eliminate the suspected precipitating factors and improve the general health of the patient. The patients invariably had psychosomatic stress, and we preferred to administer a herbal preparation.[15] The only indication of oral/topical corticosteroid in vitiligo should be galloping VI-stage. Adrenocorticotropic hormone (ACTH) injections (20-40 I.U.im) weekly should be preferred as a short course.[16] We strictly resist giving psoralens in VI-stage, as initially the whole body requires restorative measures. And only after all the system is toned up, there is logic in stimulating melanocytes. Placental extract either topically,[17] or by intramuscular route (biweekly) can also be given in VI-stage. Oral or topical L-phenylalanine cream can be alternatively used.[18,19] With such a conservative regimen, VI-stage is likely to enter a stable V2 stage in 2 to 4 months.

Once the control of the disease is achieved (V2-stage), and the borders are hyperpigmented, psoralen or Ammi majus, therapy can be started. It can be given by oral or topical route on alternate days followed by sun or UVA exposure. Pigmentation gradually enhances to the whole patches in the next 2-3 months (V3 stage).

In late V3 stages, when no further pigmentation can be anticipated, Thin Thiersch's grafts[21], can be undertaken to achieve a cure. It will also prevent the ugly tanning and ageing of the remainder of the skin by prolonged injudicious use of psoralens.

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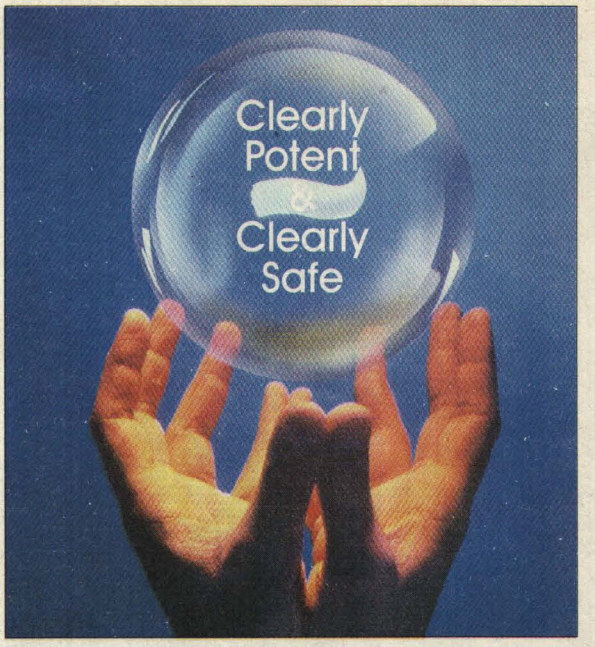

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