

Report on the Workshop: Worldwide perspectives in vitiligo

IPCC Sapporo, May 12, 2008, 11h15-12h15.

Organizers : M Picardo/ A Taïeb

Faculty/ Panel of discussants: R Boissy, R Spritz, C Goding, D Bennett, Z Abdel Malek, S Shibahara D Parsad, JP Ortonne, L Larue, Y Gauthier

Patient Support's Groups: A de Pase

Opening the workshop, A Taieb and M Picardo highlighted that 0.5% of the world population with vitiligo has unmet and mostly unrecognized health needs. They indicated the main aim of the IFPCS special interest group on vitiligo, which they chair, which is bridging scientists and physicians efforts to improve management with the help of patient's support groups. The first symposium was held 2005 at the last IPCC Reston, USA, and the minutes are available on the ESPCR website at <http://www.espcr.org/espcr/vetf.htm>

In Sapporo, the main goal of the workshop was to make dermatologists and pigment cell scientists interact about facts observed in true patients and animal/experimental models of the disease. Drs Taieb and Picardo hoped that new ideas should emerge for research and to improve patient's care.

- **Challenging clinical observations in the vitiligo clinic**
Chairs: Spritz, Bennett and Boissy

Does vitiligo fit theories of somatic mosaicism? (Taieb).

Clinical findings in vitiligo challenge the widely accepted organ specific autoimmune pathomechanisms. Based on Blaschko's lines dermatoses revisited by Happle, Dr Taieb draws the attention to the fact that the distribution of segmental vitiligo (SV) fits in at least a subset of patients a pattern usually associated with cutaneous mosaicism. The association of SV to non segmental vitiligo (NSV) now confirmed by several observations indicates a continuum between the two subsets with shared predisposing genetic factors, including genes operating specifically in the skin. Some pedigrees associating SV and NSV further suggest a mechanism of loss of heterozygosity for a dominant gene controlling part of the cutaneous phenotype. SV

would be a good candidate disease to explore as a proof of principle of a new gene discovery strategy useful for multigenic disorders with organ specificity, applicable in priority to chronic inflammatory skin disorders.

Discussion: R Spritz highlighted the transition from focal to generalized vitiligo, which can be a problem to classify patients; somatic mosaicism has frequently been suggested and rarely proven; CGH arrays to be performed. D Bennett suggested a role of SV as a trigger of NSV in some predisposed individuals.

The challenge of marginal repigmentation stop and of the post graft refractory depigmented rim (Gauthier)

Based on his observations and that of others that under repigmenting regimen marginal repigmentation is more limited than perifollicular repigmentation. Dr Gauthier suggests that: following exposure to UVR, excessive amount of melanin causes spread limitation from the margin. Differences between marginal and perifollicular repigmentation would result from already pigmented melanocytes in the former and amelanotic melanocytes from outer root sheath in the latter. In a second step due to melanin accumulation, perifollicular repigmentation would become similar to marginal repigmentation and stop. This hypothesis is reinforced by *in vitro* work (Libow, 1988 ; Abdel Malek, 1994) reporting inverse correlation between pigmentation and proliferation of melanocytes. This hypothesis is supported by the piebald guinea pig model which shows that pigment lightening agents including topical corticosteroids improve repigmentation.

The refractory rim after melanocyte grafting is established after failure of many sessions of melanocyte transplantation. This « no melanocyte's land » is always observed after grafting of post halo nevus leucodermas and inflammatory vitiligo patches. Dr Gauthier favorite hypothesis is that of a clinical marker of a previous autoimmune process.

Discussion: C Le Poole suggested a role for tenascin for inhibiting melanocyte migration. Dr Gauthier indicated that so far biopsies have not been obtained in this context.

- **Models to study vitiligo**

Chairs: Boissy, Goding, Shibahara

Animal models (Erf)

Dr Erf underlines that appropriate experimental animal models have become an essential tool to delineate and dissect the relative contributions of these genetic, immune and environmental components of chronic auto-inflammatory disorders..

She demonstrated the spontaneous autoimmune vitiligo described in the Smyth line (SL) chicken recapitulates the entire spectrum of clinical and biological manifestations of human vitiligo, providing unique opportunity to examine processes prior to expression and throughout progression of the disease. The SL chicken is characterized by a spontaneous, vitiligo-like, post-hatch loss of melanin producing pigment cells (melanocytes) in feather and choroidal tissue. Vitiligo occurs in approximately 80 to 95% of hatch-mates, with about 70% of those affected expressing complete depigmentation in adulthood (>20 weeks of age). In addition to vitiligo, SL chickens exhibit uveitis, often resulting in blindness (5 -15%), and have associated autoimmune diseases such as hypothyroidism (4 to 8%) and an alopecia areata-like feathering defect (2 to 3%). An environmental trigger is of major importance, the herpesvirus of turkey (HVT): the incidence of SL vitiligo by 20 weeks is far higher with HVT-administration at hatch. Inflammatory bacterial cell wall products (lipopolysaccharide, LPS; muramyl dipeptide, MDP) directly injected into the feather of vitiligo-susceptible non-HVT-vaccinated SL chicks can trigger depigmentation and triggers vitiligo. The process is inflammatory as assessed by immunohistochemistry. Cyclosporin has a transitory effect. Transmitted antibodies to the progeny do not induce vitiligo.

Discussion: The role of bacterial and viral infection in human vitiligo was discussed, but there is little supporting evidence so far. Sunburn could be an environment trigger with a role of HSP (Boissy).

Reconstructed human skin model (Cario-André)

Dr Cario André explained that pigmented epidermal reconstructs are a useful model to study pigment disorders even if some limitations exist such as a short lifetime. This model allows the production of chimeric epidermis with normal keratinocytes and normal melanocytes; or normal keratinocytes and non lesional vitiligo melanocytes; or vice-versa. Non segmental vitiligo cells can be obtained from non lesional skin. Vitiligo melanocytes attach with difficulty to plastic and dead dermis. In this model, basal cells are weakly attached to the basement membrane, and stressed melanocytes detach without friction. Macroscopic pigmentation is lighter in reconstructs made with non lesional vitiligo melanocytes than in those made with normal melanocytes originating of individuals from similar phototypes, due

to a significant decrease in the number of basal melanocytes. Interestingly, non lesional vitiligo keratinocytes also induce a significant decrease in macroscopic pigmentation whatever the type of melanocytes.

Some decompartmented sera from vitiligo patients induce melanocytes detachment within three hours of action. This detachment has been observed whatever the type of melanocytes (normal or vitiligo). Sera inducing melanocytes detachment induced a decrease in E-cadherin expression in all types of reconstructs.

Since vitiligo melanocytes are more difficult to grow than normal melanocytes, and since effect of stressors is similar on vitiligo and normal melanocytes, normal epidermal reconstructs could be used instead of vitiligo reconstructs to test stressors.

Discussion: Dr Le Poole wanted to know if vitiligo keratinocytes are truly important in this model. Indeed, they aggravate the vitiligo phenotype in vitro

- **Confronting patient and doctor's perspectives**
Chairs : Ortonne, de Paise

Quality of life in Asian patients affected by vitiligo (Parsad)

Vitiligo is particularly disfiguring for people with dark skin and carries such a social stigma in Indian society that patients are considered unmarriageable. Society greets vitiligo patients in much the same way as it does any one else who appears to be different. In some parts of India, they are still started at or subjected to whispered comments, antagonism, insult or isolation. A woman with vitiligo may face numerous social problems and experience great difficulties in getting married. In case a woman develops vitiligo after marriage, it grounds for divorce by the husband. In some parts of India, disease is often considered as a punishment by God, presumably caused by unconscious feelings of guilt. Patients are subjected to various dietary restrictions like avoidance of milk, fish, citrus fruits etc. In a study of 150 vitiligo patients, Dr Parsad and colleagues assessed the nature and extent of the social and psychological difficulties associated with the disease and their impact on treatment outcome by using Dermatology Life Quality Index. They clearly demonstrated that patients with high DLQI scores responded less favorably to a given therapeutic modality. These results suggest that additional psychological approaches may be particularly helpful in these patients.

Papadopoulos et al have shown that counseling can help to improve the body image, self-

esteem and quality of life of patients with vitiligo and has as well a positive effect on the course of the disease.

The point of view of the patient (de Pase)

Alida de Pase is founder of ARIV (Associazione Italiana Ricerca Informazione Vitiligine) a patient-driven, non-profit organization based in Italy and representing the interests of those affected by vitiligo. With other patients groups from around the world, ARIV takes part in the International Vitiligo Consortium and is involved in the European Vitiligo Task Force, providing participants for studies and contributing to scientific meetings.

She reported and testified the voices, experiences and hopes of vitiligo patients that go through the same experiences in all countries and what it truly means, physically and emotionally, to have this disease, that affects about 100 million patients around the world, taking no account of gender, age of onset, race, social status or life-style.

Chronic, disfiguring, pervasive and always extremely evident to the patient, by virtue of its unpredictability it continually changes the way sufferers see themselves, day by day destroying self-esteem and confidence. The disease in some cultures becomes a valid reason for divorce, in all cultures may influence the decision not to have children, for fear of passing it on. Patients may experience stigma, loneliness, bullying at school as children and problems at the work site and in daily life as adults. As a consequence, emotional pain, avoidance behaviour, depression may go on for a lifetime.

The Sapporo International Vitiligo Symposium has given the patient the possibility of assuming an active role, interacting with all the experts and specific researchers present from all over the world. Working together does make sense: patient groups can help, providing access to a broad patient base from which new research possibilities could be drawn, and encouraging research.

She concluded stressing that there is need of improved allocation of resources for this chronic disfiguring disease, and that more investment in research at a both scientific and clinical level is needed.

Concluding remarks

The organizers thanked all participants and discussants and indicated that vitiligo will be a top priority for the next IPCC 2011 organized in Bordeaux (France) www.ipcc2011.org