"Progressive hyperpigmentation and generalized lentiginosis without associated systemic symptoms: a rare hereditary pigmentation disorder in south-east Germany."

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Abstract
Familial progressive hyperpigmentation is rarely described in the literature. We report on five patients from three different families presenting with a peculiar progressive pigmentary disorder. The patients show a progressive diffuse, partly blotchy, hyperpigmentation, intermixed with scattered small hypopigmented macules, a few large hypopigmented areas, occasional café-au-lait spots and, most remarkably, a generalized lentiginosis. Histology revealed different degrees of basal layer hyperpigmentation and pigment incontinence, also in the spots appearing hypopigmented. Ultrastructural analysis showed a normal mode of Caucasian-like melanogenesis with varying content of regular melanosome complexes within the keratinocytes. All families are clustered in a small area around the town of Teublitz in south-east Germany with about 20,000 inhabitants, suggesting a genetic founder effect. Pedigree analysis is compatible with an autosomal dominant mode of inheritance with variable penetran...
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Case reports

Case 1

An 8-year-old boy (Fig. 1A), his sister aged 17 (Fig. 1B) and their father, a 54-year-old male (Fig. 1C), presented to our outpatient clinic with a peculiar pigment phenotype. Their complexions were dark with skin type III. The boy had incipient signs of blotchy, but mainly diffuse hyperpigmentation, but did not have lentigines, oral lesions or hyperpigmented palmar creases. A few large hypopigmented macules 15 cm in diameter, resembling the hypopigmented ash-leaf macules in tuberous sclerosis, were also present. The sister showed a more intense diffuse and blotchy hyperpigmentation, along with hypopigmented macules producing a confetti-like aspect. Several café-au-lait spots were noted and she had numerous lentigines spread over the whole body, but still sparing the oral mucosa and the palms. The father presented with the fully developed stage of skin discolouration. Diffuse and blotchy hyperpigmentation was even more pronounced. He showed confetti-like hypopigmentation, similar to his daughter. Disseminated lentigines covered the whole skin surface, including the mucous membranes and the conjunctivae, and several café-au-lait spots were found mainly on the trunk. Careful clinical examination and laboratory work-up of all affected family members showed no signs of any associated illness.

It was reported that the mother of the 54-year-old male had the same pigmentary disorder, suggesting an autosomal dominant mode of inheritance (Fig. 2A).

Light microscopy examination of H&E sections from the hyperpigmented areas displayed strong basal layer café-au-lait macules, large ash-leaf-like white macules and multiple lentigines dispersed over the whole integument, including the palms, soles, oral mucosa and conjunctivae. This constellation of features is unique and does not correspond to any of the aforementioned entities. We have documented the progressive clinical changes over several years and performed a preliminary analysis of the mode of inheritance.
hyperpigmentation of the epidermis and a few melanophages around the superficial blood vessels, but no increase in the number of melanocytes within the epidermis. Sections from a hypopigmented macule also showed a slight basal hyperpigmentation of the epidermis, but virtually no melanophages around the upper-dermal vessels. Ultrastructural investigation displayed varying amounts of regular mature melanosomes and complexes (Fig. 3).

Case 2
A 36-year-old Caucasian woman, skin-type III, dark hair and green eyes was referred to our department with a pigmentary disorder. Her skin showed a partly diffuse and partly blotchy hyperpigmentation with various shades of brown. In addition, disseminated confetti-like hypopigmented macules were observed, and her entire integument, lips and oral mucosa displayed numerous lentigines up to 1 cm in diameter. Typical café-au-lait macules on the trunk and hyperpigmented palmar creases were also present (Fig. 1D – F). Further clinical examination and extended routine laboratory work-up including blood cell counts, leucocyte subtype analysis by FACS and microscopy of buffy coat cells, clotting studies, platelet function tests, bleeding time and oxidative burst of neutrophils did not reveal any associated abnormalities. There was no history of neurological symptoms such as epilepsy or mental retardation; nor had she any history of repeating...
infections, as might be expected if lysosomal function were disturbed. The patient reported that the skin disorder has been noticed already at birth, but the widespread lentiginosis became apparent around the age of 14. Both the diffuse and blotchy hyperpigmentation, as well as the hypopigmented macules, progressed slowly during adolescence. Her mother, her mother’s sister and her maternal grandmother, as well a sister of this grandmother, had the same skin changes (Fig. 2B). Seven years later, the patient presented asking for laser therapy of new café-au-lait macules. Her skin showed progression of the diffuse hyperpigmentation strongly contrasting with the hypopigmented spots. Lentigines had also strongly increased in number. Light microscopy and ultrastructural analyses revealed changes similar to case 1.

Case 3
A 20-month-old girl presented with widespread slightly hyperpigmented coalescing macules mainly located on the trunk, legs, ano-gluteal area and, less prominently, on the face and upper extremities. Her appearance was similar to the boy in case 1. The mother reported that the discolouration had started at the age of 7 months and had steadily progressed. This child was seen by a paediatrician, ophthalmologist and cardiologist; furthermore, an extended routine laboratory work-up was carried out, but no evidence of any associated symptoms could be detected. Seven years later, we saw this girl again. Her physical and mental development was normal. She displayed massive hyperpigmentation sparing only the face, while the hypopigmented areas had regressed. Café-au-lait-like macules were present, but there was no discolouration of the palms, soles or oral mucosa. No family history was reported, but clinical examination of 2 sisters, aged 17 and 21, revealed some large café-au-lait spots (Fig. 2C). Light microscopy and ultrastructural analysis were consistent with cases 1 and 2.

*Fig. 3. Histological and ultrastructural evaluation of case 1. A The biopsy of a hyperpigmented spot shows pronounced epidermal hyperpigmentation and numerous melanophages (arrows) due to pigment incontinence. B In a sample from a hypopigmented appearing macule there is also a slight basal hyperpigmentation of the epidermis, but virtually no melanophages in the upper dermis. C Ultrastructurally the specimens from a hyperpigmented area showed predominantly densely packed stage IV melanosome complexes within the keratinocytes (K). D The same pattern, but fewer melanosome complexes, can be seen in the hypopigmented areas. M: Melanocyte.*
DISCUSSION

The phenotype in all these patients was characterized by diffuse hyperpigmentation, which varied in intensity. Areas clinically interpreted as hypopigmented turned out to also be slightly hyperpigmented, but less than adjoining areas. Café-au-lait macules and larger hypopigmented ash-leaf macules were also present. With time, the development of widespread lentiginosis paralleled the progression of the blotchy hyperpigmentation. The complete lack of associated symptoms suggests a pathogenesis restricted to melanogenesis-related functions. In contrast to some previous descriptions of similar conditions, electron microscopy did not show a pattern of large dispersed melanosomes in keratinocytes as seen in black skin (4, 5), but just varying content of normal, mostly complexed melanosomes, typical for Caucasians.

Therefore, this cluster of index patients from one, perhaps genetically partly isolated, enclave in southeastern Germany, may represent a rare variant in the spectrum of progressive familial hyperpigmentation disorders without associated symptoms (2, 4, 5, 9, 10). Differentiation from similar reported cases is difficult; the spectrum is highly diverse and a multitude of names have been generated in the past (1–8). Among those descriptions, the 38-year-old Italian woman with progressive hyperpigmentation described by Betts et al. (5) seems to best resemble our patients. This woman had an almost uniformly deep bronze-brown skin colour with numerous superimposed darker spots resembling a mild generalized lentiginosis which also involved the palms, lips and oral mucosa. Ultrastructural examination revealed dispersed large melanosomes typical of black skin, which we did not observe.

Dyschromatosis universalis hereditaria (7) is characterized by sharply demarcated brown macules of various sizes on diffusely hypopigmented skin, typically involving the head, anterior chest, abdomen and extremities mostly without involvement of palms and soles. The lesions are known to progress throughout the first decade of life. The patients are otherwise healthy (7, 8). Just as in our cases, the histology reveals varying pigment content of the basal epidermis and sometimes pigment incontinence. However, café-au-lait macules, larger hypopigmented ash-leaf macules and widespread lentiginosis, including palms, lips and conjunctivae, are not typical features of this condition, making it possible to distinguish such patients from ours.

A further possibly related disorder was reported by Reed et al. (11), who described a family with partial “albinism”. The skin of affected individuals was in part “achromic” and in part hyperpigmented showing round, oval, polycyclic or geographical spots and patches leading to a mottled appearance. The colour varied from light yellow-brown to deep brown-black. However, in contrast to our series, the hair was typically completely white or yellow, and lentigines were absent.

By pedigree analysis, an autosomal dominant pattern of inheritance with variability in expression and reduced penetrance can be assumed. Pedigrees A and B in Fig. 2 suggest a high penetrance (near 100%), whereas pedigree C shows larger differences in expressivity. As the pedigrees are relatively restricted in size, interfamilial penetrance difference does not exclude a common origin of the phenotype, i.e., a shared mutation. For many genetic disorders, strong variability in penetrance and expressivity has been identified even for the same mutation. Thus, assuming common ancestry of the genetic defect, we are preparing a whole genome linkage scanning of all affected individuals to identify a possibly mutated chromosomal region. This would narrow down candidate genes, which could finally give insight into the molecular pathway responsible for the phenotype and further our understanding of the mechanisms regulating pigmentation.

REFERENCES