Original articles

Hypopigmented skin alterations resembling tuberous sclerosis in normal skin

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Abstract

The significance of hypopigmented skin findings as manifestations of the gene for tuberous sclerosis (TS) in near relatives of TS patients is a difficult problem. We therefore studied the number and kind of whitish skin alterations found in 100 medical students and 100 school children. Ninety three percent of the former and 79% of the latter had some whitish lesions, many of them scars. Twenty percent of the adults and 12% of the children had roundish or oval macules larger than 10 mm in diameter, not known to be scars.

In clinical practice with TS patients, our attention has been drawn to whitish raised masses or streaks in their first degree relatives. These were also found in study subjects so the significance of such lesions remains unclear.

The role of Wood's light turned out to be questionable, far from pathognomonic for TS; 25% of all the whitish findings and 53% of the hypopigmented macules larger than 10 mm in diameter showed distinct or brilliant fluorescence under Wood's light.

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Key words: tuberous sclerosis; hypopigmented skin macules; Wood's light.

Tuberous sclerosis (TS) is classically thought to be a dominantly inherited disorder. As such, however, its behaviour is very inconsistent and bizarre. The pleiotropic features of TS are extremely variable. More than 80% of cases are reported to be the result of a fresh mutation.¹⁻³ Indeed, in a family one seldom sees two or more seriously affected sibs. Even molecular genetic studies have not so far solved the dilemma of transmission and expressivity.⁴

In clinical practice the diagnosis of TS is not usually difficult in an index case with overt symptoms and signs. However, it is not at all easy to find out whether the TS gene of the patient has come from one of the parents or whether the disease really is caused by a new mutation. This knowledge, however, is imperative for genetic counselling. One crucial question is whether some expression of the TS gene might be hidden in the seemingly unaffected parents or sibs.

Hypopigmented skin macules are one of the most common features of TS, though alone

they only indicate a suspicion of TS.⁴ As they are visible, they are probably the manifestations looked for first and most often in the parents and healthy sibs. On careful inspection, some whitish alterations are often found on their skin. However, those who have not had much experience with TS may have great difficulty in interpreting such skin findings. The more TS patients we have seen, the stronger the suspicion has become that some of these hypopigmented alterations could be of significance. On the other hand, an ungrounded belief in such findings as expressions of the TS gene would lead to a too high recurrence estimate. The right interpretation of hypopigmented skin alterations is also important in linkage studies of the TS genes in order to know who is affected and who is not.⁵

To solve this problem it is important to know what kind of whitish lesions are to be found in normal skin. Investigations of this subject are few and limited. Hurwitz and Braverman⁶ studied, in a children's hospital, the skin of 100 neurologically normal patients and 55 children with some neurological disease other than TS. They found one hypopigmented spot. Kennedy and Kalish⁷ investigated the skin of 100 newborn infants with ultraviolet lamp. They found depigmented macular lesions in four infants (0.4%), who all remained neurologically normal. Debar and Richardet⁸ studied the skin of 9737 infants, aged 1 to 18 months, in order to find out whether hypopigmented spots might serve as a sign of TS. One or two spots, larger than 1 cm², were found in 68 infants (0.7%), who developed normally. Three infants had three spots or more; of them, two probably had TS and one had neurofibromatosis. Alper *et al*^{9,10} investigated 4641 newborn babies for birthmarks and found one or more hypopigmented areas in 35 newborns (0.8%). At follow up of six infants, the light areas had disappeared in all of them. No classification or pictures of the lesions were presented.

In our study we wanted to elucidate this problem further and notably to widen the scope towards adults and children older than infants, according to the clinical demands of TS families.

Subjects and methods

We investigated the skin of 100 unselected Finnish medical students (aged 19 to 23 years, 55 females and 45 males) and 100 pupils in the first two grades of a primary school (aged 7 to 9

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Table 1 The number of subjects with different hypopigmented skin alterations

Findings	Adults (n = 100)	Children (n = 100)
No findings	7	21
Macular or raised roundish patches, probably remnants of chicken pox or acne, diameter <3 mm	49	36
Macular roundish patches, not known to be scars, diameter 3–10 mm	22	20
Macular roundish or oval patches, not known to be scars, diameter >10 mm	20	12
Raised roundish patches (masses), not known to be scars, diameter >3 mm (figure G–I)	14	17
Raised longish streaks, not known to be scars (figure J–L)	6	5

years, by chance also 55 females and 45 males).

The examination was performed standing up and in underwear, first in normal bright light and then, after five minutes' adaptation in darkness, under Wood's ultraviolet light (Original Hanau Fluotest type 5320/306A, the given wavelength 366 nanometers), which is said to make the TS hypopigmentations clearly visible. The hypopigmented alterations found were photographed by Olympus OM2N camera and flash on Fujichrome 100 colour diapositive film. The alterations were measured and classified according to their size, shape, location, and appearance under Wood's light.

None of those investigated had a history of epileptic seizures.

Results

The total number of hypopigmented lesions found was 467, 0 to 9 per person. The essential data on the quantity, size, and shape of the lesions are given in table 1. The reaction of different lesions exposed to ultraviolet light is given in table 2.

About half of all the lesions were macules at skin level. The other half were more or less raised from skin level and the majority of these were scars. However, 20% of the adults and 12% of the children had roundish or oval macules larger than 10 mm in diameter and not known to be scars.

Fourteen macules were detected under Wood's light but were afterwards also seen in normal light. Twelve macules were seen only under Wood's light; one of them could be washed off.

The location of the lesions corresponded fairly well to the relative area of different parts of the body, except that the upper extremities were represented more often. Because on examination all subjects were in underpants and the female adults in bras and pants, most of the covered areas remained uninspected.

In addition, striae were found in six adult females and six adult males. Two subjects, one adult and one child, had a clear cut dermatological disease. No lesions resembling facial angiofibromas ("adenoma sebaceum"),

shagreen patches, white freckles (confetti depigmentation), or real vitiligo were found.

Examples of findings compared to the lesions chosen from skin pictures of TS patients and their clinically unaffected parents or sibs seen for genetic counselling at the Department of Medical Genetics, the Family Federation of Finland Väestöliitto, are shown in the figure.

Discussion

The design of the study corresponded to the usual clinical situation: the school children represented TS patients and their unaffected sibs and the students represented the parents. Also the clothing of those investigated was similar to that in clinical practice as healthy relatives are seldom inspected in the nude.

The first result was that whitish skin alterations are surprisingly common in healthy subjects. Nearly all adults (93%) had something whitish on their skin. Macules less than 3 mm in diameter may very often be remnants of chicken pox or acne. As nearly half of the subjects had such lesions, they must undoubtedly be excluded from the diagnosis of the TS gene. Macular lesions more than 10 mm in diameter were found in a fifth of the adults and an eighth of the children.¹¹ The figure shows that they can even resemble the classical ash leaf or lance-ovate pattern of TS.¹² The lesions can also display pigmented islets between the hypopigmented areas, as the hypopigmented patches of TS often do.⁶ However, multiple lesions of these kinds were not seen in either study group.

Many clinical texts convey the impression that fluorescence under Wood's light is more or less pathognomonic of the hypopigmented alterations of TS, and that the inspection of patients and their relatives is not valid without Wood's light. This proved to be untrue. In normal subjects, 25% of all the whitish findings and 53% altogether of the macular patches with a diameter greater than 10 mm showed distinct or brilliant white fluorescence under Wood's light. However, the Wood's light helped to detect 26 lesions in healthy people. One of the lesions was probably some cosmetic substance because it could be washed off. We know this phenomenon also from clinical practice and Kennedy and Kalish⁷ reported it in their study. On the other hand, the study confirmed our clinical impression that whitish scar tissue often turns dark or reddish under Wood's light. As one result of this study, we are inclined to consider the value of Wood's light as not very important in diagnosing TS.

In our clinical practice with parents of TS patients, we have paid a lot of attention to peculiar raised hypopigmented masses in the

Table 2 The percentage of hypopigmented skin alterations according to their appearance under Wood's light

Findings	No or slight white fluorescence	Distinct or brilliant white fluorescence	Dark or reddish
All findings (n = 467)	55	25	20
Findings other than evident scars (n = 164)	56	41	3
Macular roundish or oval patches, diameter >10 mm (n = 43)	37	53	9
Surgical scars (n = 48)	31	13	56

Hypopigmented skin alterations of study subjects (upper row), unaffected parents or sibs of TS patients (middle row), and TS patients (bottom row). Ash leaf or lance-ovate macular hypopigmentation (A–C). Hypopigmentation with pigment islets around follicles (D–F). Raised hypopigmented roundish masses (G–I). Raised hypopigmented streaks (J–L). The tab with a number is 12 mm in diameter.

skin. They can be roundish or oval (figure G–I), but sometimes they are like a raised streak (figure J–L). Fryer *et al*³ also noticed atypical raised patches and “curious white or yellow linear streaks” in TS parents. They regarded them as artefacts. Usually the parents claim that such lesions are not scars from some known injury. According to this study, both streaks and roundish or oval raised whitish masses can also be found in normal skin.

In 20 years’ clinical counselling work at one department of medical genetics, a strong impression arose that TS, after all, might not be the result of a new mutation as often as is claimed. The main reason for this was the different hypopigmented skin findings in the otherwise unaffected parents or sibs of TS patients. This study, however, does not support our impression.

In his classical book, Gomez² regards hypomelanotic macules as not definitely, but presumptively or provisionally, diagnostic for TS in people who have a first degree relative with a definite diagnosis of TS. In his revision of the diagnostic criteria⁴ he adheres to the same opinion, although hypomelanotic macules alone are included in the weakest or suspect group of diagnostic features.

This study shows that there are many different kinds of whitish alterations in the skin of healthy people. It means that in the search for gene carriers among close relatives of TS patients, conclusions about carriership are not to be drawn too hastily. On the other hand, this study does not exclude the possibility that in some cases hypopigmented skin findings may after all be expressions of the TS gene in seemingly unaffected relatives.

The loss of heterozygosity found in TS hamartomas in patients with the TS gene linked to chromosome 16p13.3 might also provide new insight into hypopigmented macules, assuming that the TS gene works as a growth suppressor in accordance with Knudsen’s two hit hypothesis.¹³ According to these authors this theory would presuppose that similar lesions could also appear in isolation. Perhaps, then, some of our skin findings in healthy people might represent such isolated lesions?

The role of whitish skin alterations as diagnostic tools for carriers of TS genes may remain unsolved until the molecular mechanisms of different TS genes are thoroughly understood.

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