REVIEW

Linear and Whorled Hypermelanosis

Vito Di Lernia, M.D.

Department of Dermatology, Arcispedale Santa Maria Nuova, Reggio Emilia, Italy

Abstract: Linear and whorled nevoid hypermelanosis is a sporadic pigmentary anomaly occurring within the first weeks of life, characterized clinically by swirls and streaks of macular hyperpigmentation following the lines of Blaschko. Histologically it shows only epidermal melanosis. Underlying chromosomal mosaicism has been demonstrated in only a few published cases. Progressive cribriform and zosteriform hyperpigmentation is considered to be the localized variant of linear and whorled nevoid hypermelanosis. We report a retrospective study on 16 children referred consecutively over a 10-year period for evaluation of segmental, linear or swirled hyperpigmentation distributed along the lines of Blashko, consistent with a diagnosis of linear and whorled nevoid hypermelanosis. Associated abnormalities were found only in one out of six patients with the diffuse form (linear and whorled nevoid hypermelanosis-type) and in none of the remaining 10 children presenting the unilateral form (progressive cribriform and zosteriform hyperpigmentation-type). A long-term follow-up did not disclose further abnormalities. The authors discuss the nosologic position of this entity with respect to hypomelanosis of Ito. Linear and whorled nevoid hypermelanosis and hypomelanosis of Ito should be not considered single entities, but be rather grouped as a heterogeneous collection of nonspecific pigmentary disorders caused by genetic mosaicism. Skin findings in these diseases can differ according to the pigmentation in the normal cell line and whether the second line contains more or less melanosomes than the normal skin of the individual exhibiting mosaicism.

The term linear and whorled nevoid hypermelanosis (LWNH) was coined by Kalter et al in 1988 to define a sporadic pigmentary anomaly occurring within the first weeks of life, characterized clinically by swirls and streaks of macular hyperpigmentation following the lines of Blaschko and histologically by epidermal melanosis without pigment incontinence in the dermis (1). Different descriptive names, including "zosteriform lentiginous nevus," "zebra-like hyperpigmentation in whorls and streaks," "reticulate hyperpigmentation distributed in a zosteriform fashion," and "reticulate hyperpigmentation of Iijima" (2–6) had previously been utilized to describe patients with this same condition. Since the article of Kalter et al, the denomination of LWNH has progressively been adopted as additional occurrences have been reported in the literature (7–12). In 1992 we suggested that instances of unilateral linear hyperpigmentation (13) which had previously been described in the literature under the name of "progressive cribriform and zosteriform hyperpigmentation" (PCZH) (14) should also be considered to be part of the spectrum of this disorder. Many authors agreed with our judgment (15–18) that PCZH does not show clinical and histologic differences with respect to

Address correspondence to Vito Di Lernia, M.D., Department of Dermatology, Arcispedale Santa Maria Nuova, via Risorgimento 80, Reggio Emilia, Italy 42100, or e-mail: vito.dilernia@asmn.re.it.
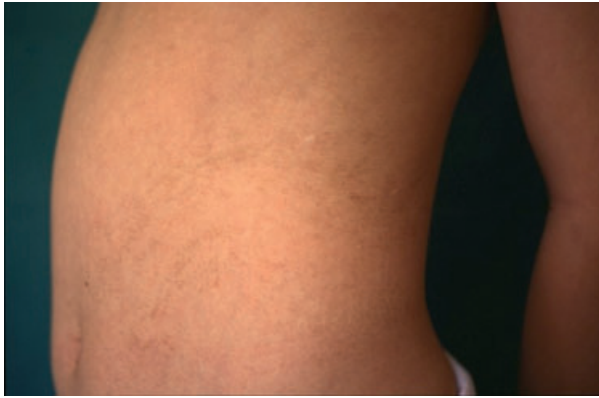
Figure 1. Swirls and streaks of macular hyperpigmentation following the lines of Blaschko on the trunk; bilaterally (patient 10).

LWNH, other than later onset, at about the second decade of life.

In this retrospective work we reviewed a group of 16 children observed in a 10-year period who presented with segmental linear or swirled hyperpigmentation along the lines of Blaschko, consistent with a diagnosis of LWNH (Fig. 1). To our knowledge, this report constitutes the largest series of patients with this pigmentary anomaly to date.

MATERIALS AND METHODS

For each child the following information was recorded: sex, age, age at presentation, distribution of the pigmentary lesions, and associated clinically relevant abnormal features. Clinical follow-up on each patient was sought yearly for 5 to 10 years. Routine laboratory investigations and skin biopsies were performed in 10 patients.

RESULTS

Linear and whorled nevoid hypermelanosis was defined as multiple swirled, nevoid streaks of hyperpigmentation without a preceding inflammatory stage. Progressive cribriform and zosteriform hyperpigmentation was defined as a localized linear band of hyperpigmentation not preceded by inflammatory lesions. Six patients had widespread hyperpigmentation of the LWNH-type, and one of these had a combination of both hyper-and hypo-pigmentation. Ten patients had a unilateral hyperpigmentation of the PCZH-type. Eight patients were male and eight were female. The patients' age at the time of referral ranged from 1 to 10 years. The abnormal pigmentation was first noted at birth in two patients and during the first year of life in the remaining four patients with the diffuse hyperpigmentation LWNH-type. The patterns of pigmentation were segmental, linear, swirled, or a combination of the above, all with a sharp midline cutoff. The pigmentation was localized to the trunk in seven patients, the extremities in six, and the head and neck in one patient. The remaining patients had widespread cutaneous involvement. Routine laboratory tests, including blood cell count with differential, were normal. In all patients, histopathologic examination of biopsy specimens showed a mild increase of melanin in the basal layer of the epidermis and mild elongation of the rete ridges. Abnormal systemic features were present in one patient affected by LWNH and consisted of severe developmental delay with autism. Follow-up examinations were carried out in all patients, however additional abnormal systemic features were not detected in any of the patients during a 5- to 10-year follow-up. One patient affected by PCZH developed in adolescence dizziness, atrophic gastritis, and anorexia nervosa. The main clinical characteristics of the 16 patients are summarized in Table 1.

DISCUSSION

The diagnostic criteria proposed by Kalter et al for the diagnosis of LWNH included an onset within a few weeks of births with progression for 1 to 2 years before stabilization; linear and whorled hyperpigmentation following the lines of Blaschko without preceding bullae or verrucae; hyperpigmented areas with increased pigmentation of the basal layer and prominence of melanocytes without incontinence of pigment; sporadic occurrence without sex predilection; sparing of the mucous membranes, eyes, palms, and soles; and possible association with congenital anomalies.

Various extracutaneous abnormalities, involving mostly the central nervous and musculoskeletal systems have been observed in a number of patients with LWNH as well as in those published earlier in the literature and reported with different descriptive names. Clinical findings include not only developmental and growth retardation, facial and body asymmetry (2,3,12,15,19–23), but also cardiac defects (24,25).

Due to the rarity of LWNH, no large series of patients affected by this condition had been studied to determine the frequency of associated abnormal systemic features until 1996, when Nehal et al reported a retrospective review of 54 patients with different conditions, including LWNH, sharing hypopigmentation and hyperpigmentation following the lines of Blaschko (26). These authors found associated abnormal systemic features, which included seizures, neurodevelopment delay, cardiac defects and hydrocephalus in four out of their group of

TABLE 1. *Clinical characteristics of the 16 patients affected by linear and whorled hypermelanosis*

No./age/sex	Type of pigmentation	First noted	Location	Additional features
1/7 years/F	PCZH	Birth	Right trunk	Atrophic gastritis, dizziness, anorexia nervosa (adolescence)
2/1 year/F	PCZH	1 month	Right buttock and thigh	None
3/2 years/M	PCZH	1 year	Trunk	None
4/2 years/M	LWNH	Birth	Diffuse	Autism, severe psychomotor delay
5/1 year/F	LWNH	1 year	Diffuse	None
6/5 years/M	PCZH	4 years	Left face and neck	None
7/6 years/M	LWNH	9 months	Trunk and arms	None
8/10 years/M	PCZH	4 years	Trunk and right arm	None
9/3 years/M	LWNH	1 year	Diffuse	None
10/4 years/M	LWNH	3 months	Diffuse	None
11/10 years/M	PCZH	5 years	Right trunk	None
12/5 years/F	LWNH	Birth	Thighs, genitalia	None
13/1 year/F	PCZH	3 months	Right buttock and thigh (flexor surface)	None
14/2 years/M	PCZH	1 year	Trunk	None
15/2 years/F	PCZH	2 years	Trunk	None
16/3 years/M	PCZH	3 years	Left arm	None

PCZH, progressive cribriform and zosteriform hyperpigmentation; LWNH, linear and whorled hypermelanosis.

13 patients with LWHN. Additional extracutaneous findings were not detectable in any of the patients during a follow-up period of 6 to 42 months. In our group of 16 patients with LWNH, we were able to find associated abnormalities in one out of six patients with the diffuse form (LWNH-type) and in none of the remaining 10 children presenting the unilateral form (PCZH-type). Although this group is too small to produce significant results from a statistical point of view, we calculated an incidence of 16% of associated abnormalities. In a long-term follow-up of 5 to 10 years we did not find additional abnormal systemic features, confirming that any occurrence of extracutaneous associated findings of LWNH is generally of early onset. In the study of Nehal et al the incidence of extracutaneous abnormalities in LWNH was 31%, thus quite similar to that of extracutaneous abnormalities found with hypomelanosis of Ito (HI) (33%).

Hypomelanosis of Ito is characterized by congenital hypopigmentation, also in a linear and whorled pattern following the lines of Blaschko. Hypomelanosis of Ito has been reported in association with neurologic deficits, epilepsy, and asymmetric abnormalities in other organs. Linear and whorled hypermelanosis resembles HI in all but the color of the skin markings. As one of our patients demonstrated, it can be difficult in extensive presentations to determine whether the basic abnormality is one of hypo- or hyperpigmentation (20). In addition, an association of both hyperpigmentation and hypopigmentation along the lines of Blaschko can be noted in the same individual (20,24–28). The concept of not strictly differentiating patients with hypo- and hyperpigmentation was implied in the series reported by Nehal et al (26). Furthermore, the association of three types of skin pigmentation, including areas with hypopigmentation and hyperpigmentation following the lines of Blaschko and normally pigmented skin, has been reported and named cutis tricolor (29–31). Developmental somatic mosaicism leading to the proliferation and migration of two mixed populations of melanocytes with different potential for pigment production was suggested as the most likely cause for the pigmentary anomalies of LWNH (1,3). Confirming Happle's hypothesis that skin disorders, including pigmentary anomalies, distributed along the Blaschko lines are the result of somatic mosaicism (32), underlying chromosomal mosaicism has been observed in LWNH, although in only a few instances (7,20,23,28,33,34). The small number of patients with LWNH who show abnormal mosaicism could be due to the fact that in most instances the karyotype was investigated in blood lymphocytes only. Indeed Hartmann et al showed that postnatal confirmation of prenatally diagnosed trisomy 20 mosaicism was possible in skin fibroblasts and not in blood lymphocytes in a patient with LWNH (25). Chromosomal abnormalities of LWNH include mosaic trisomy 7, 14 and 18 as well as X-chromosomal mosaicism. In addition, Thomas et al (35) evaluated a series of eight personal patients with pigmentary anomalies reminiscent of incontinentia pigmenti (IP) and at least 36 similar patients reported in the literature. In all instances abnormal lymphocyte karyotypes with chromosomal mosaicism of lymphocytes and skin fibroblasts, either in combination or separately, were discovered. As no histologic examination was performed, a possible diagnosis of LWNH cannot be excluded in some patients of the Thomas' series reported as having third stage IP without a history of preceding bullous or verrucous lesions.

Figure 2. Unilateral brown macular hyperpigmentation with sharp mid-line demarcation on the trunk (patient 3).

Figure 3. Two patches of unilateral cribriform brown macular hyperpigmentation on the trunk without a history of preceding eruptions, consistent with a diagnosis of PCZH.

On the basis of these observations, LWNH appears to reflect underlying genetic mosaicism for highly variable genetic defects. This disorder should be not considered an entity, but rather a nonspecific pigmentary disorder caused by genetic mosaicism as well as HI, to which it appears to be pathogenetically related (36). Of interest, a particular chromosomal abnormality can lead to LWNH or HI, as in the case of trisomy 20 (25). Thus, HI and LWNH should not be considered as distinct entities, but rather as one entity—in which these skin findings differ according to the pigmentation in the normal cell line and whether the second line contains more or less melanosomes than the normal skin (20). The coexistence of lighter and darker skin areas reflects mutant cells relative to non-mutant cells, leading to different cell lines with different variable pigment content of melanosomes (25,27). The term "pigmentary mosaicism" has been suggested as a better descriptor for these conditions (36) which, as Nehal et al point out, "should not be considered distinct syndromes but rather grouped as a heterogeneous collection of disorders indicative of underlying genetic mosaicism" (26).

In 1992 we suggested considering LWNH and PCZH (13,14) to be related conditions with variable time of onset. Although the lack of associated cutaneous and internal abnormalities was one of the suggested criteria for the diagnosis of PCZH in the original description by Rower et al, neurologic, skeletal, and cutaneous anomalies were observed by Schepis et al (17) in a patient with PCZH as well. No associated abnormalities were found in our series of 10 patients with PCZH-type hyperpigmentation (Figs. 2 and 3).

Finally, if we agree that both LWNH and HI represent pigmentary mosaicism, by analogy, the same is likely to be true of more localized and segmental forms of pigmentation such as PCZH and segmental nevus depigmentosus. Bonifazi et al suggested the existence of an "inverse" nevus depigmentosus and coined for it the term "hyperchromic nevus" (37), a term which is well accepted in the Italian/European literature, but still does not appear in the American literature or in the major dermatology textbooks (Table 2).

While significant confusion remains in the literature about the correct classification and denomination of pigmentary anomalies along the Blaschko lines these patients' findings provide further evidence of the need for a revised nomenclature or a classification of this group of disorders under the rubric of "pigmentary dysplasia with genetic mosaicism" or "pigmentary mosaicism" to encompass different phenotypic expressions of common pathogenetic processes due to genetic abnormalities that specifically disrupt expression or function of pigmentary genes.

TABLE 2. *Classification of linear pigmentary disorders distributed along the Blaschko lines*

Disorder	Pattern of pigmentation	Distribution	Mosaicism	Associated abnormalities (incidence)
LWNH (Fig. 1)	Hyperpigmentation	Diffuse	Yes	≤30%
HI (Fig. 4)	Hypopigmentation	Diffuse	Yes	≥30%
PCZH (Fig. 3)	Hyperpigmentation	Segmental	?	Very low
Segmental nevus depigmentosus (Fig. 5)	Hypopigmentation	Segmental	?	Very low

LWNH, linear and whorled hypermelanosis; HI, hypomelanosis of Ito; PCZH, progressive cribriform and zosteriform hyperpigmentation.

Figure 4. Hypomelanosis of Ito: linear and whorled hypopigmented patches along the Blaschko lines on the trunk. The distribution of the patches is the same as that of LWNH.

Figure 5. Segmental nevus depigmentosus involving the left side of the body. The distribution of the patches is the same as that seen in PCZH.

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