Association of Dermal Melanocytosis With Lysosomal Storage Disease

Clinical Features and Hypotheses Regarding Pathogenesis

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**Background:** The potential association of dermal melanocytosis with lysosomal storage disease in infancy is an uncommonly known and poorly understood entity.

**Observations:** We describe 2 infants with extensive dermal melanocytosis in association with GM1 gangliosidosis type 1 and Hurler syndrome, respectively. A literature analysis revealed 37 additional cases. Clinically, dermal melanocytosis associated with lysosomal storage disease is characterized by extensive, blue cutaneous pigmentation with dorsal and ventral distribution, indistinct borders, and persistent and/or “progressive” behavior. GM1 gangliosidosis type 1 and Hurler syndrome are the most common underlying disorders associated with these cutaneous features.

**Conclusions:** In the appropriate clinical setting, an unusual presentation of dermal melanocytosis in an infant may be a cutaneous sign of an underlying lysosomal storage disease. The pathogenetic mechanisms behind this association remain to be elucidated.

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**METHODS**

We evaluated 2 infants with extensive DM associated with GM1 gangliosidosis type 1 (GMG) and Hurler syndrome (HRL). Skin biopsy specimens from both lesional and clinically unaffected skin were obtained for histopathologic and electron microscopic examination. In addition, we conducted a literature analysis, which revealed 37 additional cases. The following information was extracted from our and previous reports: patient ethnicity and sex, DM distribution and behavior, and associated LySD (Table).

**RESULTS**

A retrospective review of the literature revealed 15 previous reports, yielding a total of 39 individual cases of DM associated with LySD including our 2 patients. Of 7 infants in whom sex was noted, the incidence of males and females was approximately equal. Dermal melanocytosis occurred more commonly among infants with darker skin types, similar to the common mongolian spot, though there was no specific ethnic predominance. Blue cutaneous patches in an extensive distribution were a unifying feature of all cases. In the majority, pigmentation involved both the dorsal and ventral trunk, often in addition to the skin of the sacrum and extremities (Figure 1). An indistinct, “feathery” border to the pigmentation was described in 3 reports. In 7 cases the pigmeny changes were noted to progress over time. No report described spontaneous regression. The most common LySD associated with DM was HRL (24 of 39 cases), followed by GMG (11 of...
Dermal melanocytosis is a histologic term that is also used to describe a clinical spectrum of cutaneous disease. These disorders are clinically distinguished from one another by characteristic location and disease course. For example, mongolian spots are typically lumbosacral in location and present at birth. In most instances this pigmentation stabilizes in infancy and then spontaneously regresses during childhood. However, in contrast to typical mongolian spots, the cutaneous pigmentation associated with LySD differs by its extensive, often anterior (in addition to posterior) location and persistent, often progressive nature. Therefore, though the term mongolian spot has been used to describe the cutaneous pigmentation associated with LySD, we prefer the more generic term DM to describe these cutaneous findings.

The pathogenesis of congenital DM is thought to reflect arrested transdermal migration of melanocytes from the neural crest to the developing epidermis. Melanocytes are embryologically derived from a stem cell population of melanoblasts that originate from the neural crest just after closure of the neural tube. In the human embryo, melanocyte migration begins at 2.5 weeks' gestation, and melanocytes have been demonstrated in the epidermis by 8 weeks on electron microscopy. Dermal melanocytes may be found throughout the integument in early fetal life, but after birth are normally restricted
to a few localized areas. These neonatal dermal melanocytes are "continent" melanocytes that retain the melanosomes that they synthesize. Normal melanocyte migration and proliferation is dependent upon exogenous peptide growth factors, which stimulate receptors with tyrosine kinase activity.

A close relationship between the nervous system (Schwann cell) and melanocyte populations, due to their common origin from the neural crest, is a known clinical entity. Melanocytes have been histologically demonstrated in close proximity to cutaneous nerve fiber bundles in several clinical variants of DM. Furthermore, at least some of these variants, such as those described as "nevus of Ota" or "nevus of Ito," are distributed along areas of cutaneous innervation.

The term "neurocristopathy" applies to disorders characterized by abnormalities in neural crest migration, growth, and/or differentiation. Dermal melanocytosis is often an associated feature of such entities. For example, multiple cases of aberrant dermal pigmentation in close proximity to clefting of the lip have been described. "Phakomatosis pigmentovascularis" applies to a subgroup of neurocristopathies in which cutaneous vascular malformations, pigmented nevi, and DM may simultaneously occur in a given patient. Similarly, patients with neurofibromatosis type 1 may develop café-au-lait macules within areas of DM.

We postulate that neural influences involving nerve growth factor (NGF) may be responsible for the arrested transdermal melanocyte migration that leads to congenital DM in LySD. In vitro studies have shown that human keratinocytes and dermal fibroblasts express NGF, which is critical for the development and maintenance of the peripheral nervous system. Melanocytes have receptors for NGF that act as a chemotropic signal for melanocytes in tissue culture; thus a defect in this mechanism could account for failed melanocyte migration.

We propose the following reason for the overwhelming predominance of DM among infants with GMG and HRL. Relative to other LySD types, these two disorders have more severe neurologic manifestations of earlier onset in infancy. Two of the accumulated metabolites of these disorders, GM1 in GMG and heparan sulfate in HRL, bind directly, tightly, and specifically to Trk protein, a high-affinity tyrosine kinase–type receptor for NGF. The binding of these metabolites to Trk, which likely occurs via glycosylation, results in an abnormal increase in NGF activity, leading to the development of large neural processes directly related to the onset, severity, and disease course of the LySD. Since melanocytes also have chemo-
tropic receptors for NGF, metabolite-Trk binding may also lead to abnormalities in melanocyte migration. In mice studies, abnormal cholesterol metabolism associated with lack of Trk function has also been proposed to contribute to the loss of neuronal function observed in Niemann-Pick type C disease.32

We previously noted that the extensive DM associated with LySD is always congenital, but in some cases also continues to develop in an unusual “progressive” manner. Although cases of “acquired” DM appearing in adulthood have been reported,31 evidence exists that this pigmentation is not truly acquired but due to the activation of previously latent dermal melanocytes. For example, melanocytes can be found by electron microscopy in the lumbosacral region in most white children but are not clinically visible because they contain inactive, incompletely melanized melanosomes.1,34 We hypothesize that the progressive DM in cases of LySD results from a similar mechanism as that of its congenital counterpart, in which metabolite-Trk binding serves as a trigger to the melanin-synthesizing pathways of dormant melanocytes.

To our knowledge, our 2 patients are the first in which biopsy specimens for electron microscopy were obtained from both lesional and unaffected skin. We observed a higher concentration of empty lysosomal vacuoles among melanocytes, fibroblasts, and Schwann-like cells among the biopsy specimens from unaffected skin. Recent electron microscopic studies of a case of GMG associated with superficial capillary-lymphatic malformations, or “angiokeratomas” within areas of DM, showed numerous cytoplasmic vacuoles within the vascular endothelial cells.5 The authors thus concluded that the angiokeratomas resulted from endothelial cell injury due to the storage of metabolic material.35 Electron microscopic study of our cases demonstrated no deposition of metabolic material or evidence of cell injury. We postulate that simultaneous with the increased metabolite accumulation and neurologic deterioration in cases of LySD, the lysosomal vacuoles are simply displaced or resorbed as melanocyte activation and clinical DM continue to progress.

Finally, aberrations in neural crest migration may result from other growth or genetic factors. Cultured human fetal melanocytes express certain homeobox genes, some of which affect the migration of neural crest derivatives when overexpressed in transgenic mice.36 Recently in a transgenic mouse model, keratinocyte expression of a hepatocyte growth factor was found to affect melanocyte migration, leading to DM. The loss of E-cadherin expression in dermal melanocyte precursors suggested that hepatocyte growth factor caused dermal localization of melanocytes and their precursors by down-regulation of E-cadherin molecules.37 The potential, even synergistic role of these or other factors in cases of LySD-associated DM requires further study.

In conclusion, our cases and those previously reported emphasize that in the appropriate clinical setting, DM characterized by dorsal and ventral distribution, indistinct borders, and persistent and/or “progressive” behavior, may be a cutaneous sign of an underlying LySD. GM1 gangliosidosis type 1 and HRL are the most common LySDs to be associated with congenital DM. The accumulated metabolites of these disorders, GM1, and heparan sulfate, respectively, are tightly associated with Trk, a high-affinity tyrosine kinase–type receptor for NGF, the binding of which enhances NGF activity and leads to severe neurologic manifestations. Receptors for NGF are also present on melanocytes, which when activated act as a chemotropic signal for melanocytes in tissue culture. We hypothesize that congenital DM and its “progressive” behavior in infants with LySD may result from metabolite accumulation, which via stimulation of NGF through Trk binding, arrests normal transdermal melanocyte migration in the dermis and may activate the melanin-synthesizing pathways of latent dermal melanocytes. Further research is needed to determine the precise mechanism by which metabolites activate the NGF-dependent Trk-associated tyrosine kinase. The potential, even synergistic role of other causative factors in aberrant neural crest migration, such as the homeobox genes and hepatocyte or other growth factors, in cases of DM in association with LySD remains to be elucidated.

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REFERENCES