Giant Melanocytic Nevus May Be Explained as a Superimposed Patchy Manifestation of a Polygenic Trait

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Key Words

Giant melanocytic nevus • Common melanocytic nevi • Polygenic inheritance • Early postzygotic mutation • Mosaic manifestation, superimposed

Introduction

Giant melanocytic nevi (GMN), defined as congenital lesions measuring 20 cm or more in diameter at adult age [1], are important because of the cosmetic burden, a frequently associated leptomeningeal melanocytosis, and an inherent risk of malignant melanoma [2]. The incidence of GMN is about 1 in 20,000 live births [3]. They usually occur sporadically but may exceptionally also show a familial aggregation. To explain this paradox, the concept of paradominant inheritance has been proposed [2].

The etiology of GMN is still unknown. Here, arguments are presented in favor of the assumption that GMN represent a superimposed patchy manifestation of a polygenic trait. This common phenotype consists of multiple small disseminated melanocytic nevi that are either present at birth or appear later in life.

Coexistence of GMN and Small Disseminated Melanocytic Nevi

Cases of GMN associated with small disseminated nevi involving the entire body have been documented with historical figures published in many articles and textbooks [4–9] and have also been reported in more recent publications [10–13]. So far, the associated small nevi have usually been categorized as ‘satellite lesions’ [4, 12, 13]. Admittedly, true satellite lesions are often noted. As a rule of thumb, such satellite nevi tend to be found within a 15-cm zone surrounding a GMN, which is reminiscent of an archipelago. By contrast, a scattered distribution all over the body (fig. 1, 2) suggests that in such cases the associated small nevi should rather be taken as disseminated ‘background lesions’. These common small melanocytic nevi do not mendelize but represent a polygenic trait [14–16]. Specifically, recent molecular research has shown that both congenital and acquired small melanocytic nevi have a common polygenic background, including mutations at the loci of *BRAF*, *N-ras*, *MC1R* and *p53* [17–20].

Fig. 1. Historical cases of GMN superimposed on small disseminated nevi. **a** Siemens and Waardenburg [4]. **b** Arzt and Fuhs [5]. **c** Sutton and Sutton [6]. Cases reviewed by Meirowsky [7]: Reinhardt, 1895 (**d**), Fox, 1912 (**e**), von Planner, 1887 (**f**), Reinhardt, 1895 (**g, h**), and De Amicis 1875/1876 (**i**).

Fig. 2. 22-year-old woman with GMN and numerous small disseminated nevi: frontal aspect (a) and dorsal aspect (b) [reprinted with permission, 8].

The Proposed Concept of Superimposed Patchy Manifestation

Common cutaneous traits with a polygenic predisposition, such as psoriasis, atopic dermatitis, or vitiligo, may sometimes manifest themselves in a pronounced linear, flag-like, or otherwise mosaic arrangement. These mosaic lesions are often associated with a less severe, non-segmental involvement and, therefore, the term 'superimposed segmental manifestation' has been proposed [21]. This type of mosaicism results either from loss of heterozygosity involving one of the predisposing genes or from a postzygotic mutation giving rise to heterozygosity at an additional predisposing gene locus. In 2009, examples of such superimposed segmental manifestation included 15 different polygenic skin disorders [22, 23].

By analogy, GMN can be taken as an additional disorder exemplifying this mechanism. For obvious reasons, however, the term 'segmental' is not always appropriate in this particular mosaic disorder (see, for example, fig. 1a, h, i, 2b). Rather, the designation 'superimposed patchy manifestation' or the less specific term 'superimposed mosaic involvement' can be applied to GMN.

Do Cases of Isolated GMN Result from a Similar Mechanism?

At this point in time it seems conceivable that a similar explanation can be applied to cases of isolated GMN. In such cases, the disseminated small nevi may develop later in life, or the polygenic predisposition, although present, may be too weak to develop a high number of common small lesions.

Is GMN Associated with a Familial Occurrence of Disseminated Small Melanocytic Nevi?

In family members of patients with GMN, an increased number of small melanocytic nevi has been reported [24]. In most cases of GMN, however, the presence of many small melanocytic nevi in relatives may so far have gone unnoticed. In future studies, special attention should be paid to this question.

Conclusion

According to the proposed concept, GMN and common small melanocytic nevi harbor similar mutations because they originate from the same polygenic predis-

position. The only difference would be that the postzygotic mutational event giving rise to GMN happens at an early stage of embryogenesis, whereas in the smaller nevi this mutational step would occur at a later developmental stage or during postnatal life.

The concept of superimposed GMN would explain why the affected newborn children often show, in addition, multiple small nevi scattered over their entire body; why they tend to develop additional small nevi during

postnatal life; why family members most likely have increased numbers of small melanocytic nevi; and why GMN usually occurs sporadically but may exceptionally involve several members of a family.

In future reports on GMN, clinicians should discriminate between true satellite lesions and the presence of disseminated 'background' nevi as reviewed in the present article.

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