Studies on Melanin.

X. Incontinentia pigmenti (Bloch-Sulzberger).

By

Minor Ito.

(伊藤 實)

(From the Department of Dermatology, Faculty of Medicine,
Tohoku University. Director: Prof. M. Ito.)

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In 1925 Bloch¹⁾ reported a case of "hitherto undescribed congenital pigmentary disturbance" in a young girl under the title of "incontinentia pigmenti". Sulzberger²⁾ made in Bloch's clinic an extensive description on this subject in 1928. Subsequently Nägeli³⁾ demonstrated analogous case with familial occurrence and named this chromatophore nevus. Siemens⁴⁾ in 1929 presented a case under the name of melanosis corii degenerativa. His case was admitted by Sulzberger as belonging to this disease. Later Bardach⁵⁾ noticed similar cases in twins. The identity of his cases with former cases was eagerly discussed by Siemens and Meirowsky-Leven, and thus attracted the attention of all investigators in the world. The number of this rare condition reported in the literature amounted to 20 including the recent report of Heilesen.⁶⁾ The first case in this country was observed by K. Kitamura⁷⁾ in 1938 and the second case was demonstrated by Yokoyama⁸⁾ at the 250th meeting of the Tokyo Dermatologic Society. The present author observed 3 cases. These are illustrated in Table I.

DISCUSSIONS.

The characteristic histologic change is the increase of chromatophores in the upper dermal layer. These belong to the endothelial or connective tissue cell origin with negative dopa reaction, and are filled with coarse melanin granules. In the basal cells in the pigmented area, the melanin content is rather decreased and various degenerative changes such as vacuolation in the protoplasm and pycnotic nuclei are noticed. In accordance with the dopa theory, Bloch and Sulzberger explained the pathogenesis of this disease in the following manner. In the normal epidermis the melanin is produced in basal cells and is mostly transported into the upper layer. In this condition the epidermis has become incontinent of the pigment and the melanin granules drop down to the corium and are

TABLE I.

Patient No.	1	2 (Fig. 1)	3 (Fig. 2)
Name	T.	N.	K.
Sex	f.	f.	f.
Age	11 months	7 months	26 years
Consanguinity and familial occurrence	None	None	None
Onset Initial eruption	10 days after birth. Erythematous eruption with intermittent fever.	Existed by birth. Erythematous exanthema.	100 days after birth. Varicelliform eruption.
Symptom	Mortar splash-like pigmentation dark brown in color with undulated zonal arrangement. Zebra-like appearance.	Bluish-brown splash-like pigment patches with marble configuration.	Slaty ashy brown pigmentation stellate in form.
Location	Symmetrically generalized.	Symmetrically generalized.	Systematized on the breast, shoulder and flexor surfaces of extremities.
Other Symptoms	Stupid appearance. Slight microcephalia and sudden death by pneumonia.	Congenital nuclear cataracta of the left eye.	Asymmetry of the breast.

phagocytized by the chromatophore. This theory was supported by Miescher who, by injection of dopamelanin to the vitiliginous area, observed that artificial melanin is sustained for a long time in the corium. Siemens accepted Bloch's theory, but at the same time assumed that the melanin production increases. In the material obtained from my third case I obtained analogous histological findings to Bloch-Sulzberger. The existence of argentaffin granules in the basal layer, as well as the negative dopa reaction in the corium, is in favor of Bloch's theory. However, owing to the rarity of this disease, there remain many questions in the etiological points which are to be solved.

In the following I try to investigate this problem chiefly in connection with the study of the nervous system.

(1) The peculiar systematized arrangement of the pigment spots in this disease was already accepted in the discussions on Bardach's case. The participation of the cutaneous nerve is naturally suspected as in cases of systematized nevi. So Voigt's borderline of the distribution of the cutaneous nerve or Blaschko's dermatome arrangement line is proposed to be the site of predilection. The location in typical cases is in arciform from the breast region to the shoulder and descends along the upper arm,

Fig. 1. Case no. 2.

quite corresponding to the Voigt's line.

(2) In usual dermatoses, the eruption is convex-bordered in accordance with the region of a vasomotor nerve, while in this disease the morphology of the larger eruption is characteristically concave contoured. How is this concave form explained? Here I tried to find some special significans. First of all the reagibility of the vasomotor nerve was examined by histamine scratch test. In the pigmented area the production of the wheal was earlier than the surrounding normal zone by 10–15 seconds. This fact suggests that there exists congenital abnormality.... an interstice either morphological or functional, in the distribution of the vasomotor nerve especially in the constrictor portion. This interstice between the segmental distribution of the vasomotor nerve is the predilection of the pigmentation, hence the concave contour!

(3) Bloch-Sulzberger stated that erythema, swelling and bullous or lichenoid eruption are seen prior to the pigmentation. The existence

Fig. 2. Case no. 3

of the inflammatory stage was observed by most investigators except Naegeli, Moncorps and Nexmand. The significance of this inflammation has not been thoroughly recognized. It is true that the inflammation may stimulate the pigment production as in the pigmentation following tear spread, arsenical intake or action dermatitis. But it is impossible to contribute such generalized occurrence of inflammation vaguely to the congenital factor only.

On the ground of afore mentioned hypothesis, the author tries to interpret this problem in the following manner.

In individuals possessed of labile autonomic nervous system, there may arise abnormal reactions in part of the vasomotor nerve to external stimuli of the extrauterine environment. These reactions give rise to inflammatory changes especially in the interstice of vasoconstrictor nerve and thus result in the disturbance of melanin metabolism. The above-mentioned acceleration of the histamine test may have disclosed the remainder of this local disposition.

(4) The pigmentation in this dermatose usually disappears by 4-5 years of age like the mongolian spot. This is explained either as the common characteristics of the dermal pigment cell or as the result of compensation through the correlation of the autonomic nervous system in the loco or through chemical transmission. This is quite corresponding to the observation of Lasser and others that systematized nevi may disappear by itself...the characteristics of the so-called neuronevus.

In my third case as well as in Sulzberger-Praser-Hutner's⁹⁾, the pig-

mentation persisted till the youth like the persistence of the mongolian spot in form of the blue nevus.

(5) In all reported cases the pigmentation is most prominent in the perimammillary region. In the case of Sulzberger-Praser-Hutner, the breast of the diseased side was smaller than the other. In my third case the left breast, where the pigmentation was much darker, was by far smaller than the right. I assume that this indicates the retarded development of this merocrine gland through the congenital asymmetric distribution of the trophic nerve, in the sense of the homolateral nervous disturbance. In accordance with this theory I observed two female cases of systematized nevi in the breast region with smaller breast on the diseased side. In another case of a 20 years old woman with hairy nevus in the breast region asymmetry of the breast was noticed. These facts as well as Lewith's¹⁰⁾ similar observation are in favor of my foregoing assumption.

The relationship between melanin production and nervous factor has been established by the experiments of Brücke, Pouchet and v. Frisch on the chameleon and the turbot. In 1932, Parker summarized these results and proposed the theory of neurohumoralism. In human being many investigators found both clinically and experimentally that there exists correlation between melanin production and cutaneous nerve. The author has already reported many observations suggestive of this point. In cases of pigmented nevus, blue nevus, Recklinghausen's phacomatosis and in pigmentary disturbance following perniosis and erythromelalgia and in vitiligo, the role of autonomic nervous system in the pigment production was noticed.

From above the author believes that the foregoing suggestions on the etiology of this disease cannot be a mere phantasy and dare to report on the paper.

CONCLUSION.

This disease occurs in individuals with congenital dysfunction on the part of the autonomic nervous system. These easily react with various grades of inflammatory changes against external stimuli of the extrauterine life. This inflammation results in the disturbance of the melanin metabolism and further in the incontinence of the epidermis. Thus the pigmentation is produced in the characteristic symmetrical and concave arrangement. But the recovery can appear sooner or later when the space is compensated by the correlation of the peripheral nervous system.

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