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Pelger-Huët Anomaly with Essential Hypertension

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本態性高血圧症を合併したペルガーホイト核異常

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要 旨

高血圧症の一女性に臨床経過中，顆粒球の核分葉異常が見出され，光顕・電顕的にペルガーホイト（Pelger-Huët）奇型が確認された。この奇型を有する家族に本態性高血圧症が合併しており，両疾患の関係を考察した。

SUMMARY

Failure of granulocytic nuclear segmentation was found in a female subject during the clinical course of hypertension. Histochemical and electron microscopic examination of the blood cells confirmed the Pelger-Huët anomaly. The pedigree showed abnormal mature granulocytes in five members of her family, and was associated with essential hypertension in three adults among them. We discuss the differences in the genetic abnormality between the two disorders. In 1928, Pelger[1] first described a failure of granulocytic nuclear segmentation and Huët[2] in 1932 disclosed the hereditary nature of the anomaly. Subsequent investigators demonstrated dominant character of the disorder by selective bleeding in rabbits[3] and later a serious hemopathy was found in human homozygous subjects[4].

Reported cases of the condition, now known as the Pelger-Huët (P-H) nuclear anomaly, are limited in number and few cases associated with other hereditary disorders have been described so far, though the disorder is probably more than

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realized. In the present patient the anomaly was combined with essential hypertension which has recently drawn attention from the genetic point of view.

CASE REPORT

A 39-year-old woman, mother of two boys, was admitted for evaluation of hypertension detected 2 years earlier. Physical findings on admission were temperature 36.4℃, obesity 135% (Broca), no struma, normal heart sounds, and pure respiratory sounds. Blood pressure was 164/98mmHg. The change in the fundus oculi was H_2So (Scheie). Electrocardiography showed no remarkable findings. The costothoracic ratio was 57% on a chest roentgenogram. Laboratory studies showed normal urine and no occult fecal blood. The hematocrit level was 40.9%, reticulocyte count 18‰, platelet count 24 X $10^4/mm^3$, and WBC $4100/mm^3$. The differential leukocyte count showed basophils 1%, eosinophils 3%, lymphocytes 32%, and neutrophils 64%. Of the neutrophils, 23% were bilobed cells and 41% were unilobed, suggesting Pelger-Huët (P-H) anomaly. Serum levels of liver enzymes, urea nitrogen, creatinine, and iron were normal. Results of autoantibody and Coombs' tests were also normal. Rheumatoid factor and ANF were negative.

Endocrinologically, peripheral levels of thyroid hormone, pituitary hormone, plasma renin activity, aldosterone, cortisol, urinary 17-KS, and catecholamine values were normal. The results of a dexamethasone suppression test were compatible with the patient's simple obesity and borderline diabetes mellitus.

Chromosomal examination disclosed no abnormality. Bone marrow aspiration showed an normal myeloid-erythroid ratio, left-shifted myelopoiesis, many P-H cells, and no ringed sideroblasts or granuloma (Table 1).

Table 1. Bone Marrow Analysis of the Patient

NCC	4.4 x 10^4	Eosin	2.8(%)
Mgk	6 /mm^3	Mono	10.4
Mbl	0.4(%)	Lym	16.4
N: Pro	10.4	Plasma	1.2
N: Myel	26.4	Ebl: Baso	3.6
N: Met	11.2	Ebl: Poly	17.2
N: St	5.6	Ebl: Orth	0.8
N: Seg	3.2	Ebl: Mito	0.4

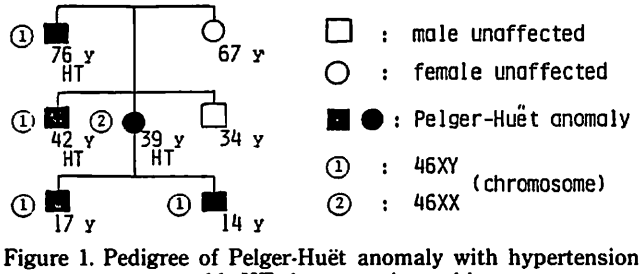

Figure 1. Pedigree of Pelger-Huët anomaly with hypertension
y: years old, HT: hypertensive subject

Because of the decreased nuclear segmentation in peripheral neutrophils and the presence of P-H cells in the bone marrow, the patient's relatives and their underlying diseases were further investigated. The patient's pedigree showed similar abnormality in five members of her family (Fig 1). In peripheral blood smears of the five members, nuclei of the leukocytes were telephone, pince-nez, or peanut form. Immature-like cells appeared as 2% myelocytes in her brother and

in two sons, and as 6-11% metamyelocytes in four members other than the patient, but no other leukemoid abnormality was found (Table 2).

Table 2. Hemogram of Peripheral Blood and Blood Pressure in 5 Members of the Family

	Patient	Son-1	Son-2	Father	Brother
Hb g/dl	13.9	14.7	13.6	15.0	15.8
RBC $x10^4$	443	477	489	529	521
WBC	4100	5800	6400	5300	8000
Myel %	0	2	2	0	2
Metamyel.	0	6	6	7	11
N{1	41	23	12	20	25
N{2	23	12	19	12	10
Baso	1	0	0	0	1
Eosin	3	1	5	8	1
Mono	0	0	0	0	0
Lym	32	56	56	53	50
Hct. %	40.9	43.8	41.4	46.5	48.5
Retics ‰	18	9	12	14	20
Plts $x10^4$	24.0	15.5	22.5	17.2	18.0
Blood Pressure	164/98	110/76	108/62	160/95	152/90

Electron microscopic examination of the blood cells revealed that most of the neutrophilic leukocytes possessed one or two lobes with well-preserved heterochromatin. A decrease in both primary and secondary granules was noted, and the cytoplasm had few Golgi structures and a scanty endoplasmic reticulum (Fig 2). The eosinophils had granules of various shapes and sizes which contained one or more crystalloid formations (Fig 3). Platelets showed a decreased number of alpha granules (Fig 4).

In a study of cell function in vitro, neutrophil phagocytosis of *Pseudomonas, Staphylococcus aureus, Escherichia coli,* and *Candida* was within normal limits (86-99%). Cytochemical study showed no remarkabale findings. Studies of qualitative leukocyte enzyme activity revealed a positive peroxidase reaction, NAP 80% positive score 236, in contrast with rate 54% score 127 in the patient's father, who had suffered from malignant fibrous histiocytosis in his leg.

Hypertension was found in the two adults with P-H. The course and degree of hypertension was mild, and it was classified as stage I-II (WHO). Secondary hyper-

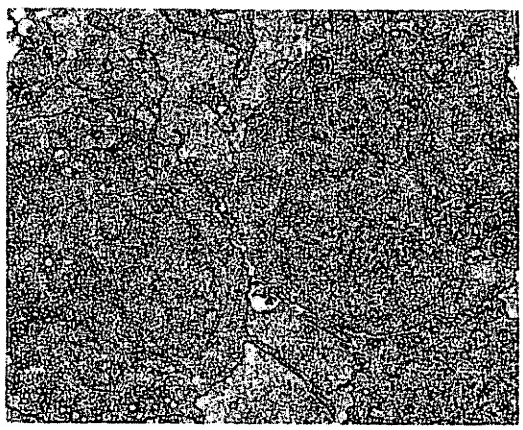

Figure 2. Electron micrograph of the neutrophilic leukocytes showing hyposegmented nuclei and decreased granular content. x 9,000.

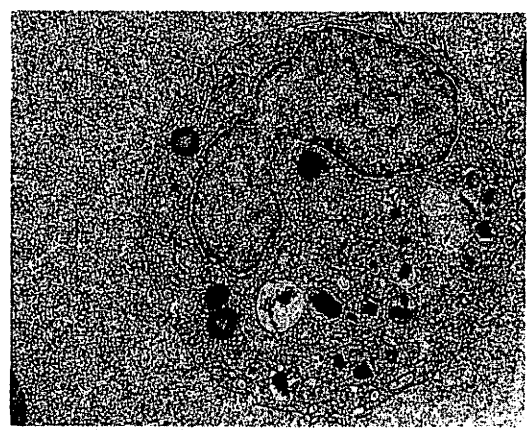

Figure 3. Electron micrograph of an eosinophil showing the polymorphism of the specific granules. x 9,000.

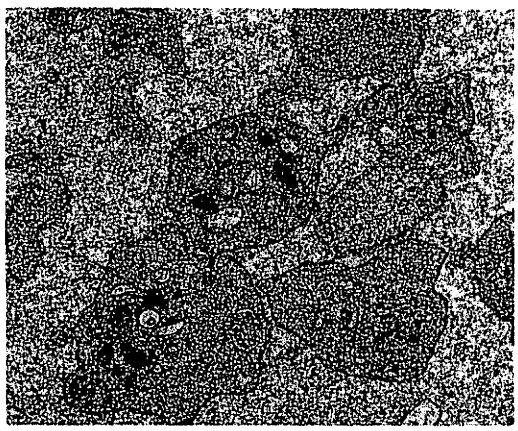

Figure 4. Electron micrograph of platelets showing decreased alpha-granules. x 18,000.

tension was excluded by endocrinological and other laboratory data.

DISCUSSION

The hereditary granulocytic anomaly described by Pelger and Huët is characterized by partial or complete failure of segmentation of the nucleus of the mature polymorphonuclear leukocytes.

The P-H anomaly is an autosomal dominant disorder occurring in about 1: 60,000 of the population. The incidence reported varies because the patients, usually free of symptoms, seem to be overlooked[5]. In Japan, at least 39 families with the disorder have thus far been reported[6]. All subjects were limited heterozygous. Although the anomaly could be lethal in homozygous subjects, only two definite cases have been documented[7].

In cytogenetic analysis, the homozygous form is marked by rounded nuclei that lack segmentation, in contrast with the heterozygous form which has rod-like, dumbbell, or pince-nez nuclei with smooth, rounded, or oval lobes. The nuclear chromatin is abnormally condensed. A possible linkage between chromosome 22p and the P-H anomaly may well be connected with chromatin synthesis[8]. In the heterozygous state, there may be an increased incidence of infection or diabetes mellitus owing to decreased chemotaxis; however, most of these patients have a benign condition with normal granulocyte count, function, and phagocytic activity.

The leukocyte anomaly in our patient was found by routine examination of a peripheral blood smear. Our ultrastructural findings in the blood cells were similar to those reported by Djaldetti et al[9]. In our case, however, no distinct nuclear bridges were observed in the neutrophilic leukocytes. A similar morphologic anomaly can occur as an acquired condition in severe myxedema[10),11], infection[12),13),14], leukemia[15], and cancerous involvement of the bones. In our patient, no signs or symptoms of such a condition were found. Her father, who had suffered from malignant fibrous histiocytoma[16] with a leukemoid reaction, has retained the P-H cell state even after the lesion was successfully treated. Pseudo-P-H cells have been reported to occur as reactions to such drugs as colchicine[17], ibuprofen[10], and others[18], but the patient denied taking any drugs. Although autoimmune defects accompanying the P-H anomaly have been reported[19], immunological studies were negative in our case. The clinical conditions may belong to type III of Harm's classification[16].

The pedigree of the family suggests an association of the essential hypertension with the adult P-H anomaly, although this anomaly does not appear to be linked to other congenital traits[9], even in young subjects. In our case, where it was associated with mild and labile hypertension, no proof of secondary hypertension was found

endocrinologically or nephrologically. Hypertension may be related to age as in experimental animal (SHR)[20], but not to obesity because hypertensive father and brother were not obese.

Multiple factors (polygene) of hypertension must be genetically clarified in humans. More than 10 genetic loci have been established in hypertensive subjects. According to Feinleib[21], approximately 60% of systolic and diastolic blood pressure has a genetic etiology potency in hypertensive twins, and 40% is associated with other circumstances[22]. Therefore, their hypertensive concordance decreased with age.

The mean age of the P-H anomaly hitherto reported appears too young to be concerned with appearance of hypertension, differing from the relation between age and hypertension in SHR. A possible effect of the P-H anomaly on blood pressure, or concordance of the two diseases in adulthood has not been thus far described.

Resultantly, we have described a case of congenital P-H anomaly (Type III)[23] combined with essential hypertension, which may need further genetic analysis. To our knowledge, this is the first reported case of a patient who has suffered from both diseases.

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