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Pathogenesis of angiodysplasias

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The pathogenesis of angiodysplasias was studied in 382 patients. Of the primary and secondary morphogenetic factors importance is attached to fetal diseases, intrauterine reparation, hormonal effects in neonatal age and early walking. It is concluded that angiodysplasias develop under the joint effect of genetic and environmental factors. They are evolutional anomalies undergoing changes in the course of life.

Genetic anomalies of the vessels are met with in every period of life. In infancy they occur in the form of naevi, haemangiomas, angiomatosis and as hypertrophic or hypoplastic extremities due to angiodysplasia. In childhood the anomaly manifests itself as a gradually developing varicosity, phlebectasia, arterio-venous shunt or lymphangioma, while in adults primary varicosities may appear. Successful attempts have been made in the last few years to present a satisfactory classification of angiogenetic malformations [17, 31, 37, 48].

In the first ten weeks of embryonic life, three stages can be distinguished in the development of the vascular system [15, 31, 41, 42, 44, 46, 50]: (1) the capillary network; (2) the retiform; and (3) the truncular stages. Some authors [17, 31] attribute the angiodysplasias to dysontogenetic processes. Disorders in the first stage may lead to capillary malformations (naevi, capillary haemangiomas); those in the retiform stage may cause phlebangiomas, arterio-venous angiomas and arterio-venous fistulae; disturbances in the truncular stage may lead to arterial and venous deformities such as agenesis, hypoplasia, anomalous vascular topography, etc.

Considering that the development of vessels, particularly that of the veins, proceeds during the whole course of fetal life and even after birth, the primary morphogenetic factor exerts its effect not only in the first phase of embryonic life but also in the fetal and postnatal periods. These malformations may significantly be modified by vascular function, blood circulation, and other secondary morphogenetic factors.

Primary Morphogenetic Factors

Followers of the genetic theory [5, 13] explain the changes by gene mutation. Some authors [27, 28]

reported the familial occurrence of congenital absence of valves in the deep veins, while others [2, 49] described the familial occurrence and heredity of cavernous haemangioma, and phlebangiomatosis has been suggested to represent a hereditary condition [32]. The familial nature of primary varicosity has been confirmed by many authors [38]. Angiodysplasias are often attributed to some endogenous and/or exogenous factors acting in different stages of ontogenesis [1, 8, 9, 10, 18, 21, 25, 35, 39, 47]. Some authors observed angiodysplasias developing in connection with embryonic lesions of the nervous system [7, 10, 16, 22, 25, 40].

In the present study including 382 patients with angiodysplasia, attempts have been made to reveal the aetiology of these alterations.

Observations

(1) The role of certain genetic informations is unquestionable.

(a) The familial occurrence of the lesion could be verified in two cases.

N.N., a 4 months old male infant from the mother's first pregnancy, had cavernous haemangiomas on the tip of the nose and upper lip. The mother displayed dysplasia of the hip and haemangiomas, a maternal aunt and the grandmother also had haemangiomas.

F.G., a 1-month-old female infant, the first child from a first pregnancy, had a vascular naevus and varicosity on her moderately hypertrophic left upper extremity. Her father, paternal aunt and grandmother also had varicosities.

(b) Considering that certain hereditary diseases are associated with angiodysplasia, the role of genetic factors cannot be excluded. Teleangiectasias occur in Osler disease, one of dominant hereditary character, and in ataxia teleangiectasia, an autosomal recessive condition. Haemangiomatosis is characteristic of the autosomal dominant syndrome of Hippel—Lindau and agenesis of the lymph vessels in the equally autosomal dominant disease, Milroy lymphoedema.

(c) Chromosome analysis was performed in 21 patients with angiodysplasia. An aberrant chromosome was found in one case of complex angiodysplasia with lymphoedema. It is, however, well known that some conditions due to chromosomal anomalies, like Turner syndrome, are frequently associated with angiodysplasias. Aortic isthmus stenosis occurs in one fifth of these cases and lymphoedema in an even higher proportion. In a Hungarian material of 48 cases of Turner syndrome angiodysplasias occurred in 22 patients: 9 had lymphoedema, 8 coarcation of the aorta, 3 lymphoedema with coarctatio of the aorta, 1 patient a congenital heart defect and 1 intestinal angiomatosis. Of our own 6 patients with verified Turner syndrome 3 had lymphoedema and 1 intestinal angiomatosis.

(2) To study the role of environmental factors we examined 7 pairs of twins of whom 2 were monozygotic.

Angiodysplasia occurred in one of them and cavernous haemangiomas were observed in one, and arteriovenous angiomatosis of the left hand in the other. This suggests the role of environmental factors in the development of angiodysplasias.

(a) The significance of teratogenic compounds has also been stressed [12] as haemangioendothelioma was observed in patients working with vinyl chloride, thorium dioxide and organic arsenicals. Liver angiomas and cutaneous haemangiomas were observed also in subjects residing in the vicinity of polyvinyl chloride plants.

(b) Drug-induced lesions have not been observed. Forty-four of the 382 mothers took some drugs, mostly phenothiazine derivatives, in the 1st to 3rd months and 23 in the 4th to 8th months of pregnancy. Mothers of the other 315 children with angiodysplasia did not take any drugs throughout pregnancy apart from iron preparations; these were regularly taken by close to 90% of the pregnants. One mother reported on taking anticoncipient pills in the 1st month of pregnancy; her child was born with venous trunk anomalies.

(c) No correlation was found between maternal diseases during pregnancy and angiodysplasia in the offspring. Four mothers were ill in the 1st to 3rd months and 9 in the 4th to 8th months; they delivered normal children. There was one exception, a mother who had contracted rubella in the 2nd month of gestation; the infection was confirmed serologically. The baby was born with a giant haemangioma on the left leg associated with thrombocytopenia (Kasabach—Merritt syndrome).

(d) Age distribution of the mothers of the patients was comparable to that of the normal population Table I.

(e) No correlation was found between induced abortion and angiodysplasias.

Fifty per cent of the patients were first children, half of them were born from first pregnancies, the others from first deliveries after some abortions. Half of the second to fourth children were also born after abortions.

(f) The conditions of delivery were studied in 324 instances. In 281 cases the delivery was uncomplicated, in 18 complicated, and in 25 instances by Caesarean section.

(g) Effect of fetal diseases. It was remarkable that patients with the same truncular angiodysplasia may have different syndromes.

F. I. and *S. T.*, male newborns, were born with congenital absence of

TABLE I

Age of mothers at birth of children with angiodysplasia

Age, year	<16	17—20	21—24	25—29	30—34	35—39	>40
No. of mothers	2	52	101	82	36	14	0

the femoral vein as confirmed by angiography. Nevertheless, one had a complete Klippel—Trenaunay syndrome, while the only symptom of the other baby was a slight swelling of the extremities. It was assumed that in the first patient the aetiological factor had acted in the early embryonic period, while in the other patient the noxa occurred much later, in the prenatal period (intrauterine thrombosis?).

Such cases can only be explained by fetal diseases, in other words certain congenital anomalies of the vessels point to intrauterine vascular diseases. Among these, intrauterine thrombosis seems to have special importance. Benirschke and Driscoll [3] found in 11 of 1718 placentas (0.64%) allantoic vessel thrombosis, once in a stillborn baby. Kloss and Vogel [24] attribute importance to several missed abortions. Klippel and Trenaunay [23] ascribed the syndrome named after them to embryonic infection. Mottled skin was observed in connatal toxoplasmosis, obliterating endangiitis in connatal syphilis and granulomatous lesions of the hepatic vessels in cytomegalic inclusion disease [24].

Secondary Morphogenetic Factors, Haemodynamic Effects

Blood circulation and haemodynamic conditions play an important role in shaping the vessels. Accordingly, angiodysplasias react sensitively to the physiological haemodynamic changes occurring at a given age.

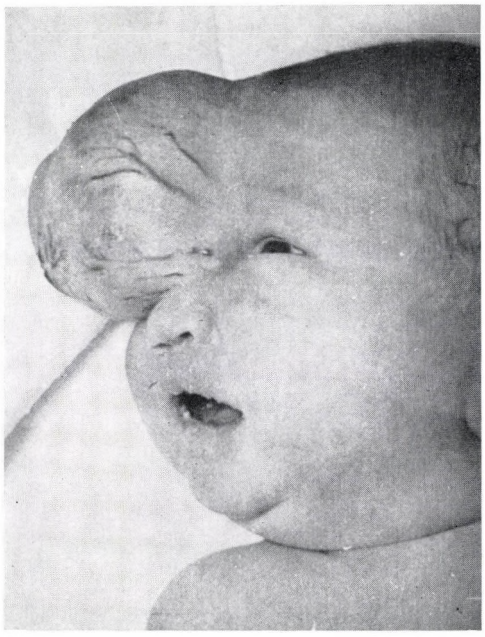

Fig. 1. Congenital arterio-venous angioma

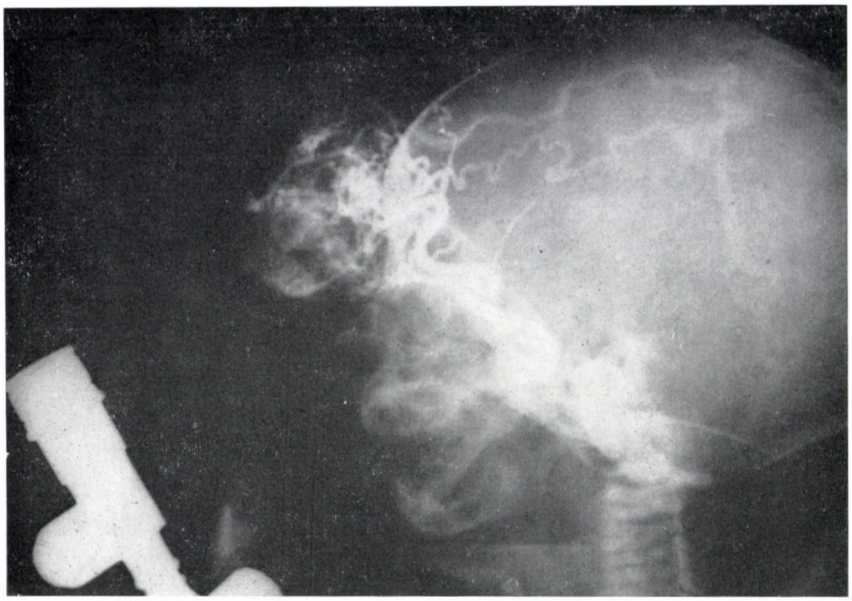

FIG. 2. Angiogram of an arterio-venous angioma

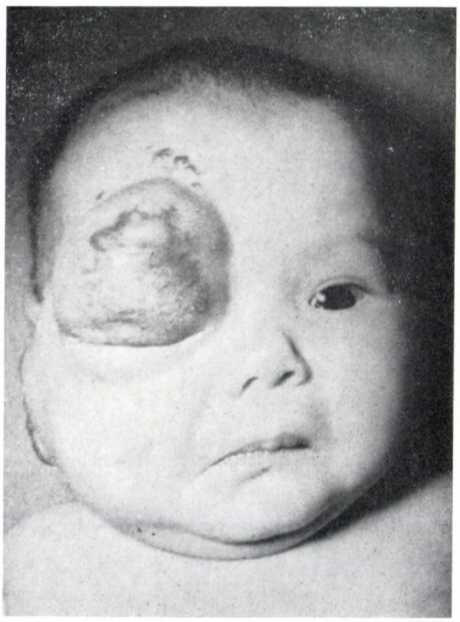

FIG. 3. Quickly proliferating arterio-venous angioma

(1) The influence of haemodynamic changes may manifest during fetal life.

K. A., a female newborn, was delivered with a giant arterio-venous haemangioma, while in *V. T.*, another female infant, the angioma developed some weeks after birth (Figs 1, 2, 3).

M. F., a male infant, exhibited congenital hypoplasia of the femoral vein. Compensatory venous dilatation could be detected at birth already: a dilated vein transported the blood from the femoral vein in front of the symphysis to the external iliac vein (Figs 4, 5).

It seems as if the defective venous flow could have been repaired before birth. Thus, similarly to intrauterine regeneration [4] a process of intrauterine reparation may also exist.

(2) Haemodynamic changes may have more importance in extrauterine life. In 165 of our 334 patients no lesion could be observed at birth (Fig. 6).

(a) Haemodynamic changes due to trauma, local infection, physical and hormonal effects may induce the growth of congenital arterio-venous angiomas and accentuate the effect of shunts [20, 36].

Hormonal effects may play a role in the development of arterio-venous angiomas indiscernible at birth but identifiable in 1 to 2 months old infants. They grow rapidly thereafter. The high serum oestradiol level of 11 400 μg/ml 2 weeks after birth, then its sudden fall to 22 μg/ml may elicit haemodynamic changes similar to those induced by hormonal activity in puberty and during the menopause. In these periods of life haemangiomas grow in number and size,

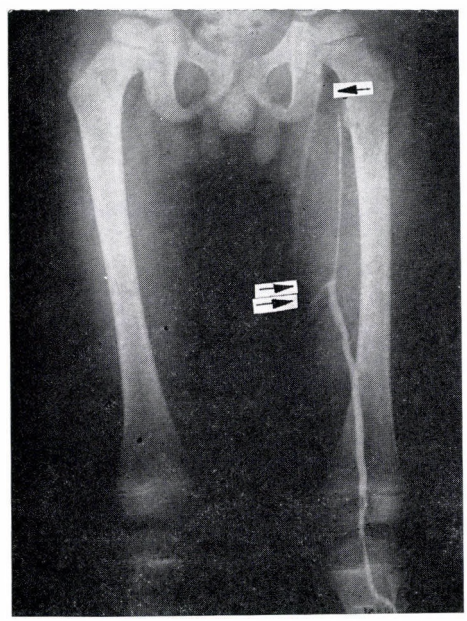

FIG. 4. Hypoplastic femoral vein. The great saphenous vein is filling from the deep vein

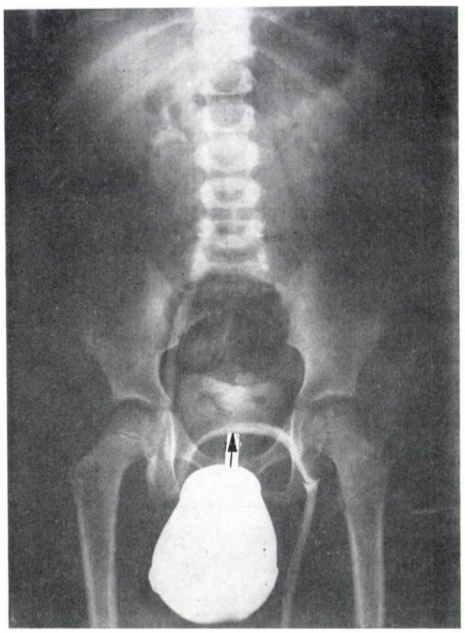

FIG. 5. From the great saphenous vein the blood is transported via a congenital compensatory vessel to the contralateral external iliac vein

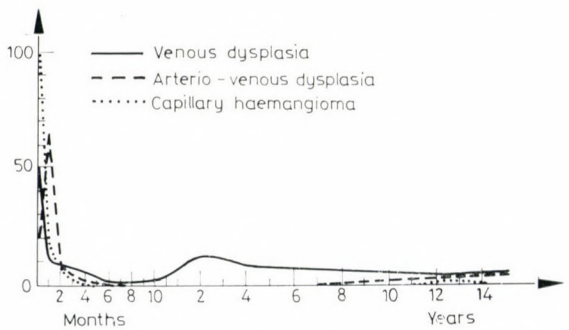

FIG. 6. Age at appearance of angiodysplasia

latent shunts may open up and in this way varicosities appear. This seems to be supported by our observation that the occurrence and quick proliferation of arterio-venous angiomas cannot be observed in preterm and small for date newborns. In such babies the oestradiol level is low and the hormonal reactions of gestation are hardly demonstrable.

(b) Prolonged haemodynamic effects may considerably contribute to the appearance of venous dysplasias [11, 19, 33]. This would follow from our observation that standing and walking increase the incidence of

venous dysplasias, assumedly by overcharging the veins of the legs. In cases of aplasia of the venous valves or after congenital venous lesions the symptoms manifest in the later periods of life under the effect of physical and hydrostatic loads [14, 29, 30, 45].

(c) The role of trauma is clearly indicated by lympho-venous angiomas. They are usually observed between 6 and 10 years of age. In such cases some trauma is regularly mentioned in the history.

In our own material there were 22 lymphatic and 4 lympho-venous angiodysplasias. Diagnosis in the latter 4 cases was confirmed by needle biopsy and angiography.

Thus, both genetic and environmental factors contribute to the development of angiodysplasias which are evolutional anomalies changing in the course of life. They are usually considered to represent minor anomalies but in view of their frequently severe consequences in later life they deserve special attention.

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