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Lymphatic Malformation in Human Fetuses

A Study of Fetuses with Turner's Syndrome or Status Bonnevie-Ullrich

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Summary. In 7 spontaneously aborted fetuses characterized by a large cystic hygroma in the nuchal region and a prominent and generalized edema, the structure and extension of the lymphatic system was studied. In all fetuses marked malformations of this system were found. Although the morphologic appearance seemed to vary greatly it is suggested that the disorder is essentially a generalized hypoplasia and partial agenesis of the lymphatic system, which ceases to extend peripherally at an early embryonic stage.

A suggestion as to the mechanism of this growth inhibition is made.

Key words: Human fetus – Congenital lymphatic malformations – Cystic hygroma – Fetal Turner syndrome – XO monosomy.

Introduction

When studying chromosomal aberrations in spontaneous abortions Singh and Carr (1966) observed fetuses among the XO-monosomy group with a highly characteristic appearance. These fetuses, which were phenotypic females, showed a combination of severe generalized edema and a large cystic hygroma in the nuchal region. They had been spontaneously aborted at a gestational age of 123 to 159 days and varied in body length from 75 to 134 mm. From this discrepancy between the true gestational age and the age estimated from the body length the authors concluded that they had been dead for quite a long period. Their findings were confirmed later by other investigators (Hienz and Gropp, 1968; Rushton et al., 1969; Singh, 1970; Planteydt and Oey, 1975). This pathological entity, apparently attended by fetal death, was considered by some to represent one extreme of the condition known as Turner's syndrome. Certain features of this latter syndrome i.e. the webbed neck and the partial

and transitory edema of the extremities were thus thought to be residual or less pronounced features of the far more serious condition in the fetus described by Singh and Carr. Although the disorder does not seem to be rare (Planteydt en Oey, 1975) only a small number of comparable case reports were found to have preceded the publication of Singh and Carr.

If we exclude incompletely described fetuses (Sömmerling, 1791; Henke, 1819; von Ammon, 1841; Everke, 1883; Vonwiller, 1886; all cited by Rössle; Meyer, 1912; and Steinfort, 1926) only 23 were found which were sufficiently accurately described to bring them into this group (Otto, 1841 cited by Rössle; Neelsen, 1882; Candamine, 1892; Rössle, 1900; Grünwald and Kornfeld, 1935; Knorr, 1951; Werthemann and Reiniger, 1949; Schweingruber, 1955; and Barthe, 1963). This pathological condition was refered to as Status Bonnevie-Ullrich by some of these authors because of the essential similarities which existed between these human fetuses and malformed mouse embryos studied extensively by Bonnevie (Ullrich 1930, 1938). Their hypothesis was questioned by some other investigators (Grünwald, 1947; Werthemann and Reiniger, 1949) and was finally abandoned by Ullrich (1949, 1951). Reports of 4 other fetuses exhibiting generalized edema together with a cystic hygroma of the neck were made by Meckel (1818 cited by Rössle), Steinwirker (1872) and Simmonds (1923), but these fetuses were phenotypic males.

There was no consensus of opinion about the pathogenesis of the disorder. Theories of hydremia and inflammation (Neelsen, 1882), amniotic strings (Rössle, 1900) and rhesus incompatability (Simmonds, 1823; Knorr, 1951) must be considered to be of historical interest only.

More recently the influence of (unknown) endogenous or exogenous agents (Werthemann and Reiniger, 1949; Schweingrüber, 1955; Barthe, 1963) or a congenital malformation of the lymphatic system (Grünwald and Kornfeld, 1935; Rushton et al. 1969; Singh, 1970) were suggested to be possible causative factors. With regard to the latter suggestion few data were available and no systemic investigation into the form and structure of the lymphatic system in these fetuses has as yet been performed. After the completion of our investigations into the normal development of the lymphatic system (van der Putte, 1971, 1975a and b) the availability of some fetuses with the characteristics described above offered an opportunity to contributing to knowledge of disturbances in the development of the lymphatic system, and to clarify a pathological condition often unrecognized by the clinical pathologist.

Material and Methods

The disorder was studied in 7 fetuses with generalized edema and a nuchal hygroma. They were born after a gestation of 148 to 184 days and varied in length from 100 to 155 mm C.R. Normal lymphatic development at earlier and corresponding developmental stages was studied in 7 other apparently normal embryos and fetuses (Table 1). All fetuses were fixed in toto in 10% formalin. They were examined as accurately as was possible without disrupting the tissues, both externally and internally. In all cases, whole section blocks were taken from both the upper arms, lower arms, hands, upper legs, lower legs and feet, and serially from the whole prevertebral region. Moreover some blocks were taken from the mesentery and intestine, lungs, liver and the thin portion of the wall of the nuchal sacs. The material was embedded in paraplast, sectioned transversally to the axial anatomic structures and stained with haematoxylin-eosin. For studying the main lymphatic-venous anastomoses and their relations to the main lymph trunks and hygromata, the lower jugular region was serially sectioned in all the malformed and some of the normal fetuses.

Table 1. Age and crown-rump lenght of malformed (specimens A–G) and normal fetuses (specimens H–O).

Specimen	Gestational age (days)	Estimated age at death (days)	C.R. length (cm)
A	184	135	14
B	168	140	15
C	186	125	13
D	?	120	11.5
E	161	145	15.5
F	182	140	15
G	148	120	10
H	63	–	3.3
J	75	–	4.5
K	86	–	5.5
L	98	–	8
M	130	–	13
N	142	–	15
O	146	–	15

Fig. 1. Fetus F exhibiting the characteristic external appearance of the malformed fetuses. Note the large nuchal hygroma and the severe and generalized edema

Results

Macroscopic Findings

Externally, all malformed fetuses were remarkably similar (Fig. 1). All showed a prominent and generalized edema with an almost monstruous, large and

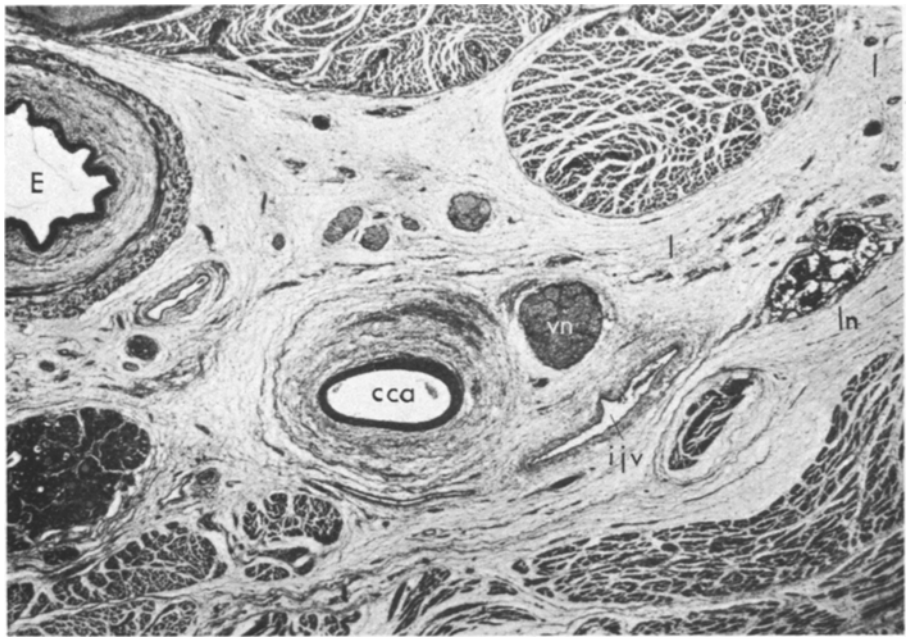

Fig. 2. Transverse section through the jugular region of the normal fetus M showing normal relations between the lymph vessels (*l*) and other anatomic structures such as internal jugular vein (*ijv*), vagus nerve (*vn*), common carotic artery (*cca*) and esophagus (*E*). Haematoxylin and eosin. ×20

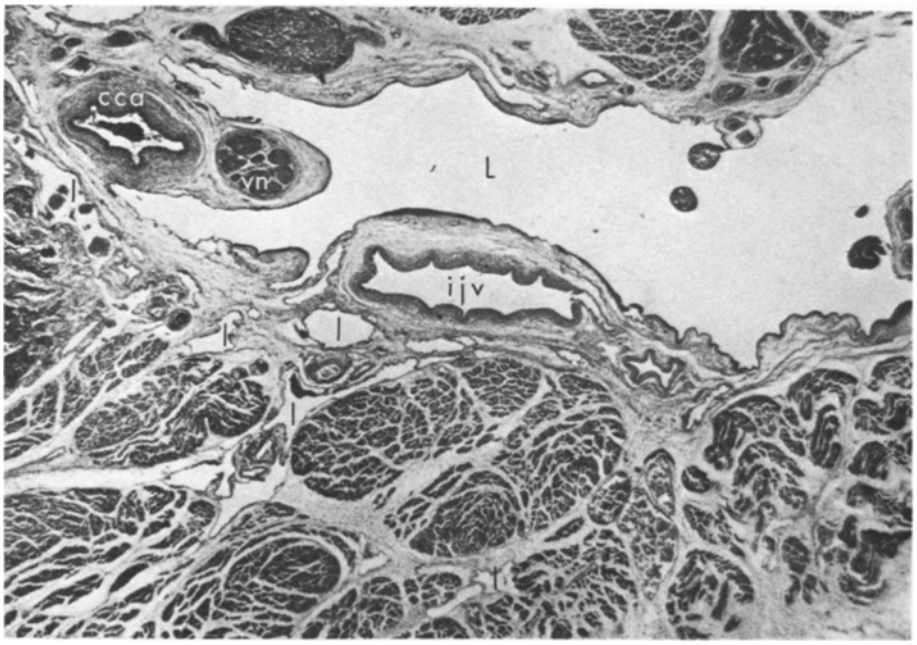

Fig. 3. Transverse section through the jugular region of fetus B. Wide medial extensions (*L*) of the nuchal hygroma split into extensive plexuses of wide lymph vessels (*l*) in the edematous connective tissue. Cf. Figure 2. HE. ×20

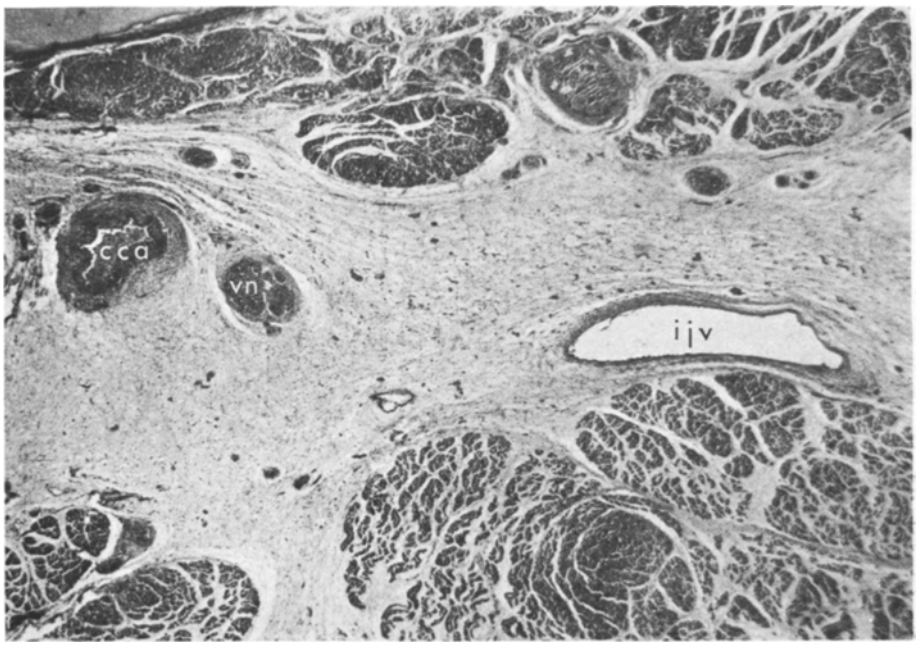

Fig. 4. Transverse section through the jugular region of fetus E. The area is completely devoid of lymph vessels. Cf. Figure 2. HE. ×20

fluctuating swelling in the posterior and lateral part of the neck; maceration was marked. They were phenotypicall females. Internally, edema was present in all connective tissues, although most prominent in the subcutaneous layers. The thoracic and abdominal cavities contained some fluid. The swelling in the neck consisted of at least two bilaterally symmetrical cavities completely separated by the nuchal ligament. In most cases each cavity was in turn subdivided into a variable number of compartments by incomplete septa. These had a smooth inner lining and contained a turbid light-brown fluid with occasionally coagulated fibrin. The cavities extended from the upper part of the occipital bone to the scapular region caudally, and medially to beneath the sternocleidomastoid muscle. For the most part they were situated superficially to the musculature of the neck with a deeper extension to the proximal part of the internal jugular vein.

In one of the fetuses (B) however, another recess was found which reached as far as the axilla and was traversed by the brachial plexus. In this fetus and in some others (A, F, G) small cysts were found subcutanously in the lateral thoracic wall just caudal to the axilla.

Gross examination of the other main systems revealed no abnormalities.

Microscopic Findings

In all malformed fetuses moderate or severe edema in combination with a marked increase in collagen was observed in all connective tissues.

Main Lymph Trunks. In normal development this part of the lymphatic system is the first to be formed. The trunks develop by fusion of a series of originally seperate lymphatic primordia which are situated prevertebrally, in embryos up to 25 mm C.R. length. The most cranial of these primordia attain a very considerable size forming large sacs lateral to both internal jugular veins with an extension under the sternocleidomastoid muscle to the subcutaneous tissue of the posterior triangle of the neck. The other lymphatic primordia fuse to form more slender and plexiform vascular structures along the main prevertebral blood vessels. Both show gradual differentiation in their walls and become interrupted by lymph nodes, while sprouts invade more peripheral tissues. The principle pattern of this part of the system has been laid down in fetuses of about 55 mm. C.R. length (Figs. 2 and 5). In the hygromata, the inner lining of cysts, which appeared to be smooth macroscopically in all fetuses, proved to be very irregular in some (A, B, C, D) by microscopic examination. In these fetuses the cavities were continuous with intricate systems of very irregular lymph channels extending in the edematous connective tissue around all adjacent anatomic structures (Fig. 3).

In other fetuses the hygromata consisted of isolated cavities, which did not continue into plexuses of lymph vessels. In two of them and on the right side of the third (G) lymph vessels were absent in the whole of the jugular and axillary region (Fig. 4). On the left side of the third cranialward extensions of the thoracic duct were found, lying closely applied to the left hygroma but not in communication with it.

The wall of the cysts consisted of a variable amount of concentric layered connective tissue. Probably as a result of maceration, no endothelial cells were found.

Despite careful examination no lymphatico-venous communications could be detected near the jugulo-subclavian junction. Complete and continuous axial lymph trunks were present in four fetuses (A, B, C, D). They were normal in position, but were distinctly abnormal in form, being much wider than normal (Fig. 6). In the upper thoracic and lower jugular region in particular they had also increased in number, showing complex and even labyrinth-like networks. The number and volume of lymphnodes seemed to be decreased, but because of great variability in number and volume (as in normal fetuses) no reliable estimations of their numbers could be made. An essentially similar configuration was observed in the abdominal and thoracic parts of the other fetuses. In the jugular and axillary region however, where no lymphplexuses occured, the thoracic ducts, paratracheal and internal mammary lymph trunks ended blindly in the loose connective tissue in front of the transverse processes of the lower cervical vertebrae, in the paratracheal area at the same level, and around the first ribs. On the left side of one of these fetuses these extensions had reached the proximal parts of the internal and external jugular veins.

Peripheral Lymphatic System. The formation of the peripheral lymphatic system was greatly disturbed. In normal development extensions of the main axial lymph plexuses start to grow out in embryos as small as 30 mm C.R. length. Lymphatic sprouts invade nearby organs, parts of the skin and the proximal

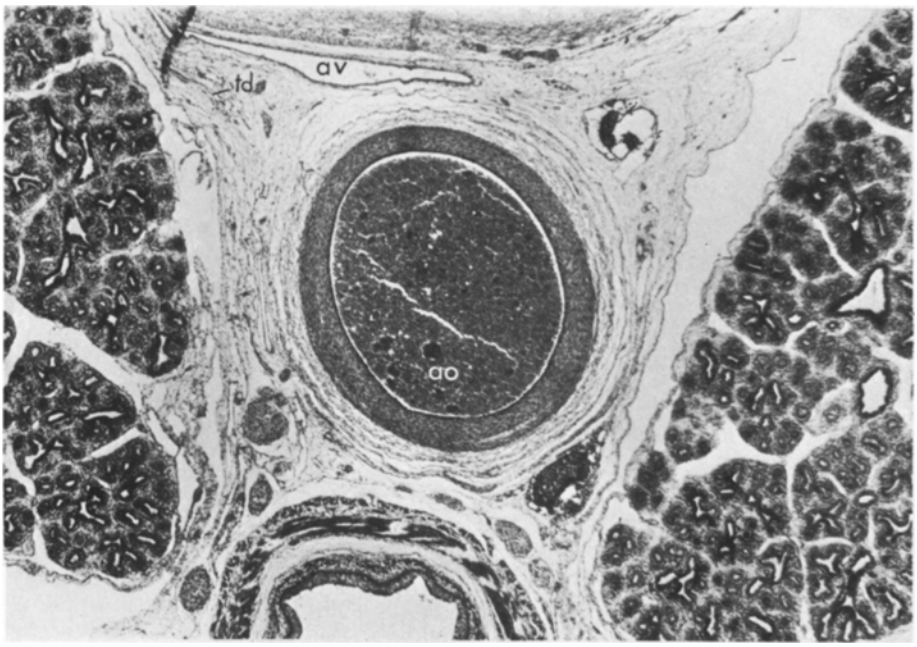

Fig. 5. Transverse section at mid-thoracic level in fetus M showing a normal configuration of the thoracic ducts (*td*), the aorta (*ao*) and azygos vein (*av*). HE. ×32

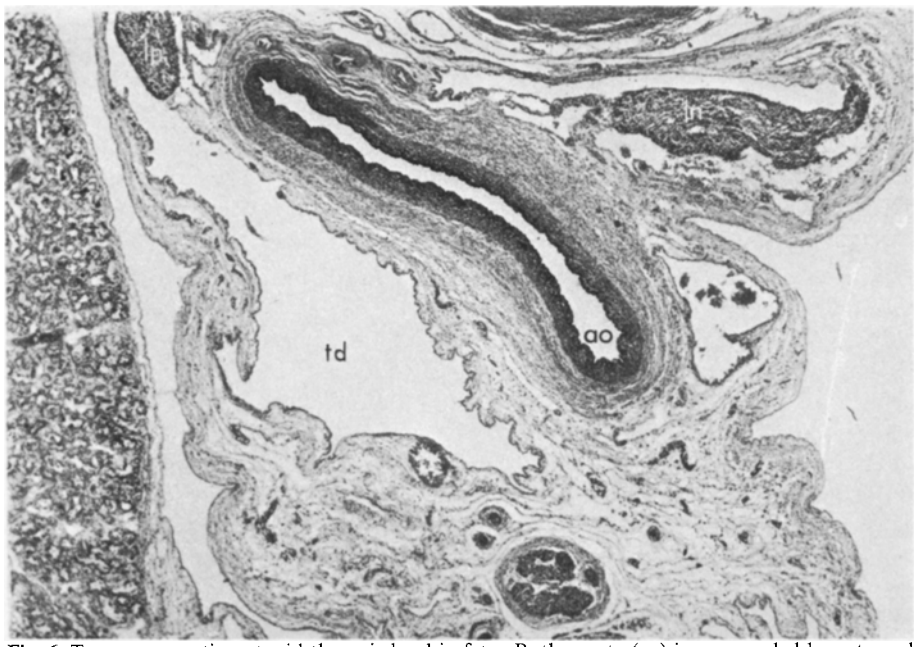

Fig. 6. Transverse section at mid-thoracic level in fetus B. the aorta (*ao*) is surrounded by extremely wide thoracic ducts (*td*). In their walls lymphnodes (*ln*) have developed. Cf. Figure 5. HE. ×32

Table 2. Form and extension of the lymphatic system in the malformed fetuses

Specimen	Main lymph truncs		Peripheral system				
	jugulo-axillary	others	body wall	lungs	arm	leg	tongue
A	++	+	++	±	++	++	±
B	++	+	++	±	++*/−	++*/−	−
C	++	+	++	±	+*/−	−	−
D	++	+	±	±	+*/−	−	−
E	−	+	±	−	−	−	−
F	−	+	±	−	−	−	−
G	−	+	±	−	−	−	−

++Dilated and numerous, +Dilated, ±Dilated and scanty, −absent, *proximal part only

parts of the extremities, mostly along blood vessels but also independantly from the latter especially in the skin. On the whole they have reached all areas in embryos no longer than 55 mm C.R. length, becoming more complicated afterwards. In the normal fetuses of developmental stages corresponding to those of the abnormal ones extensive and finely structured networks of lymph vessels have formed. They communicate with large trunks which are provided with valves and lymphnodes. In selected parts of the malformed fetuses the following observations were made (Table 2).

In none of the fetuses lymphatics had grown into the *tongue*. In one some dilated vessels were present, but these did not extend beyond the very base of the tongue. In the *lungs* two grossly different pictures were seen. In some of the fetuses (E, F, G) the larger part of the lungs was totally devoid of lymph vessels and only in the hilar region were rather uncomplicated networks of lymph vessels present. In all others lymphatics had spread all over the lungs but their pattern was abnormal being too few in number and too wide in diameter. In the hilar area only a few rather small lymphnodes had developed.

It was considered probable that in the *liver* and *mesentery* similar appearances would be found, but due to serious maceration, no definitive observations could be made.

The configuration of the lymph vessels of the *dorsal* and *lateral bodywall* was also disturbed. In this area, which is supplied with lymph vessels from plexuses along the intercostal and lumbar blood vessels, only two fetuses (A, B) had formed cutaneous tributuaries. These were too wide (A) or, in addition, too complex (B). In all other fetuses extensions of the intercostal and lumbar vessels did not extend beyond the deep connective tissue just superficial to the muscular fascia, where they often exhibited angioma-like features.

Most accurate observations were made in studying the lymph vascular patterns in the *arms* and *legs*. In normal development in embryos of about 25 mm C.R. length lymphatic sprouts from the axillary and iliac lymph plexuses start to invade the arms and legs respectively. Although some grow out along the blood vessels, most of the lymph plexuses in the extremities are formed by direct extension into the deeper layer of the skin. They have reached the tips

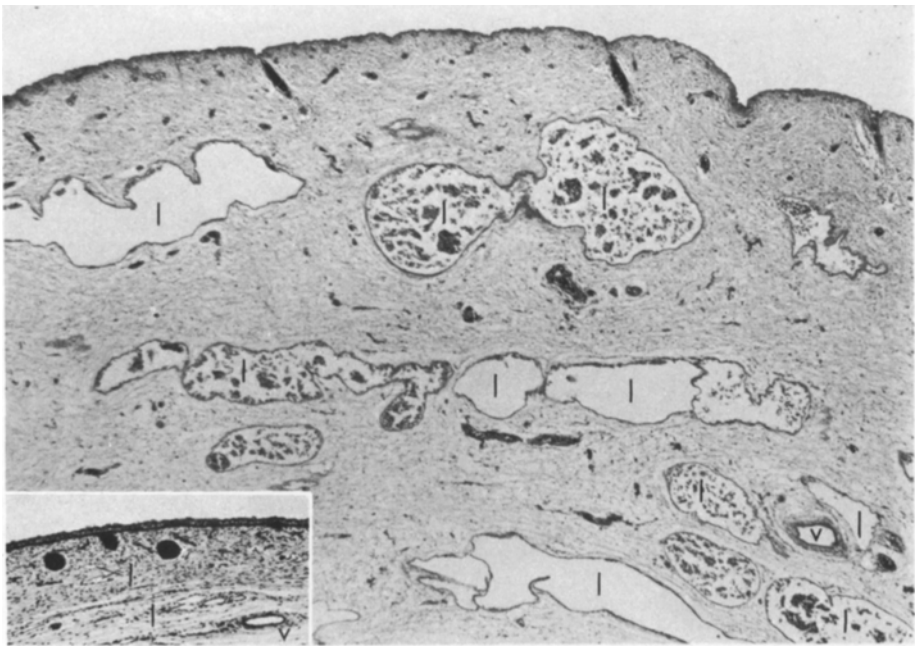

Fig. 7. Transverse section through the upper leg of fetus B. In the dense and edematous subepidermal connective tissue irregular networks of extremely wide lymphatics (l) are shown. *v* vein. Inset—the normal configuration at the same magnification. HE. ×32

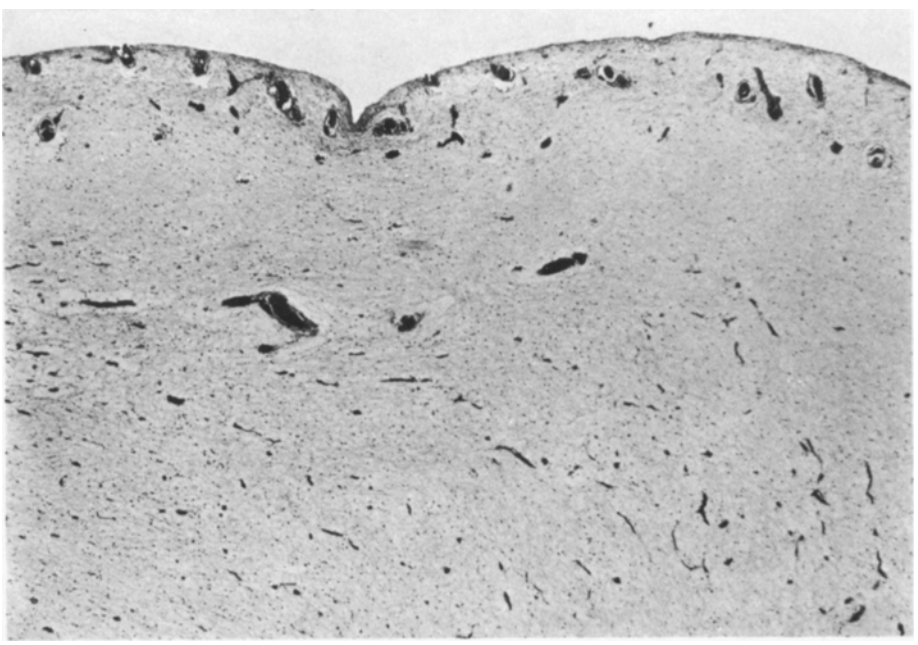

Fig. 8. Transverse section through the upper leg of fetus E. In the dense and edematous connective tissue of the skin lymph vessels are absent HE. ×32

of the fingers in 45 mm and the tips of the toes in 55 mm embryos. In fetuses of stages corresponding to those of the malformed ones examined here, relatively fine-meshed networks of lymphatics have spread all over the extremities. They are situated just under the developing adnexal structures of the skin and communicate both with some longitudinal trunks in the subcutis and with plexuses of lymph vessels along the deeper blood vessels.

In extremities of the malformed fetuses striking abnormalities were encountered, of a very variable nature. In one there were exaggerations of normal development with greatly increased numbers of very wide lymph vessels (Fig. 7) throughout the extremities both in the skin and in the deeper layers. Normal valvular structures were absent. By contrast, in three fetuses all extremities were found to be completely devoid of lymphatics, except for the most proximal part of the leg of one of them.

The other fetuses held an intermediate position. One was comparable with the first mentioned in terms of the form and structure of the vessels but differed in the degree of extension, as the lymph plexuses ended at the level of elbow and knee. In two other fetuses wide lymph vessels, often no more than a small group, were observed only in the upper arms and no lymphatics could be detected in the legs (Fig. 8).

Discussion

This investigation was directed less towards problems related to the XO chromosomal status and its various morphological modes of expression, than to the study of the lymphatic system in fetuses in which congenital malformations of this system might be expected. The tissues did not permit karyotyping; however a search for sex chromatin in the cells of the amniotic lining was unsuccesful in 3 fetuses (A, C, D).[1]

No indications of rhesus incompatability as suggested by Simmonds (1923) and Knorr (1951), nor to endogenous or exogenous toxins as suggested by Werthemann (1949), Schweingrüber (1955) and Barthe (1963) were found. As far as could be established without causing too much damage to the fetal tissue, no gross abnormalities were present in the major organ systems. Thus the edema and the malformations of the lymphatic system seem to represent the main anatomical disorder in these fetuses and certainly explain their external appearance. As in all previous investigations the edema was found to be prominent and generalized. It was associated with a marked increase in connective tissue as in longstanding lymphedema in children and adults. From clinical studies in less marked but probably essentially similar conditions after birth (Benson, Gough and Polani, 1965; Alvin et al., 1976) the edema has been considered to be the result, rather than the cause, of the inadequate lymph drainage.

The generalized character and seriousness of this protein rich lymphedema may well support the idea of Seller and co-workers (Seller et al., 1974; Seller, 1976) that the raised levels of alpha-fetoprotein in the amniotic fluid of XO-

[1] This test was performed by H.T. Planteydt, Pathological Laboratory, Middelburg, The Netherlands

fetuses with cystic hygromata are due to leakage of serumcomponents from the fetuses. Unfortunately nothing is known about the permeability of the fetal epidermis and mucous membranes for this protein. But perhaps a parallel may be drawn with the loss of protein through the mucosal lining of the intestinal tract secondary to intestinal lymphangiectasia in adults (Pomerantz and Waldmann, 1963).

The lymphatic disorder in these fetuses consists of malformation of both the main lymphatic trunks and the more peripheral system. Of these malformations the changes in the jugular region are most obvious, because of the presence of the hygromata. In the literature the hygromata are therefore most accurately described (Rössle, 1900; Grünwald and Kornfeld, 1935; Knorr, 1951; Schweingrüber, 1955; and Barthe, 1963). As far as macroscopic examination is concerned, no real differences were found between earlier observations and those described here. Microscopic investigations have been few and comprised (in most papers) a study of small pieces of the thin portions of the sac, showing mostly lymph vessels between the dermal layer and the sac itself (Simmonds, 1923; Barthe, 1963; Heinz and Gropp, 1968; Rushton et al., 1969). A few investigations supplied data about relations to the median jugular anatomic structures (Rössle, 1900; Grünwald and Kornfeld, 1935; Knorr, 1951). In all these studies, the hygromata were found to be continuous with very extensive and wide plexuses of lymph vessels which surround all anatomic structures of the neck, a configuration quite similar to the one found in 4 of the fetuses in this study.

It is important to note that these findings do not differ essentially from those found in the more detailed microscopic-anatomical studies of the more anteriorly situated and more common hygroma colli cysticum (Paetzold, 1906; Nast-Kolb, 1907; Simmonds, 1923; Bucher, 1934; Goetsch, 1938 and Gross, 1948) and the cystic hygromata occuring in the axillary, mediastinal and retroperitoneal region (Childress, Baker and Samson, 1956; Hermanutz, Bold and Frotscher, 1975). No previous observations were encountered which are comparable with those made in three fetuses here, which possessed only simple sacs without angioma-like extensions into the surroundings. Furthermore, these three cases seem peculiar since no continuity was found to exist between the hygromata and the rest of the lymphatic system. Taking into account the normal development of the lymphatic system (van der Putte, 1971, 1975a and b) this configuration may be explained by an assumption of serious underdevelopment of the jugulo-axillary lymph sacs. However, we should also consider the possibility that in these cases the jugular and axillary lymph sacs have completely failed to develop and that the hygromata have been formed by accumulation of fluid in intercellular spaces of the subcutaneous connective tissues, a situation found in pigs (in press). The last supposition may also be true for the cysts sometimes found in the lateral thoracic wall.

No systematic study of the configuration and structure of the other main lymph trunks and more peripheral system in these fetuses has been made. In the tissues studied previously, which were mostly taken at random from the skin, all investigators but one (Schweingrüber, 1955) observed a marked increase in the number and diameter of the lymph vessels. In contradistinction,

the findings in this study differed greatly from one fetus to another and from one part to another in the same fetus, varying from total absence or decrease in number of lymph vessels to almost angiomatous configurations. These differences had apparently had no effect on the external appearance of the fetuses. Indeed, looking over the whole of the lymphatic system in all of the fetuses this difference does not seem to be fundamental, because even in those fetuses with parts exhibiting hyperplastic features other parts are as "hypoplastic" or "aplastic" as cases with generalised hypoplasia.

In all fetuses the abnormalities of the lymph vessels themselves are essentially the same: they have grown out in more or less abnormal patterns and are too wide and thin walled, possessing few or no valves. It seems highly probable that the basic disorder is an underdevelopment of the lymphatic system which may locally become expressed, paradoxically, as a form of hyperplasia.

We can only speculate on the cause of the disturbed outgrowth. It may well be intrinsic to the lymphatic endothelium and related to a chromosomal disorder, but one may also think of other extrinsic mechanisms which influence lymphatic outgrowth. From the experiments of Clark and Clark (1932) it is known that the outgrowth of lymph vessels may be seriously hampered by mechanical factors. Too high a pressure or too great a density of the tissues to be invaded may inhibit growth, or cause complete arrest. If the same mechanism operated in embryonic development, impairment of lymph flow would thus lead to a sort of vicious circle consisting of impairment of lymph flow, lymphedema with structural alterations of the connective tissue, inhibition of lymphatic outgrowth, a further diminution of lymph drainage, more lymphedema, etc. The final outcome then may be a complete inhibition of the extension of lymphatics, resulting in hypoplasia and localized agenesis.

Such a series of events may be the results of a retardation in the development of the early lymphatic primordia, as demonstrated in the pathogenesis of congenital hereditary lymphedema in pig (van der Putte, in press). In these human fetuses, however, such a process could not be demonstrated as decisive stages were not available. The absence of the normal lymphatico-venous communications in the jugular region, never-the-less, may well provide an alternative cause for impairment of lymph flow and lymphedema. Unless other lymphatico-venous communications between the lymphatic primordia and the veins take over, the disappearance or marked hypoplasia of these openings would cause an increasingly serious and generalized lymphedema.

The period in development involved may well be determined by comparing the incomplete extension of the peripheral lymph vessels in the defective fetuses with the normal rate of peripheral outgrowth. Nothwithstanding considerable variability, it was established by this method that inhibition of outgrowth had started, at its latest, when the embryos had reached a C.R. length of 30 to 35 mm (gestational age about 10 weeks). This is about (or shortly after) the time that the definitive lymphatico-venous communications are formed. As a consequence, differences in the time of onset or in the rate of maldevelopment of these anastomoses may be reflected in the degree and rate of impairment of lymph drainage and thus in the ultimate degree of extension of the peripheral lymphatic system. In accordance with this theory the peripheral outgrowth

is almost negligible in those fetuses which show the most serious defects in the jugular region.

Paradoxically, the frequently observed tendency of the lymph vessels to group together and to form angiomatous structures may also be explained by the same mechanism. For one may assume that in the immediate vicinity of newly formed lymph vessels more favorable conditions exist which allow a certain degree of lymphatic sprouting and extension for some time. At the same time, at some distance from the vessels, changes are taking place which will obstruct later outgrowth.

This pathological process may be a highly characteristic reaction of the lymphatic system to obstruction and/or delayed outgrowth during its early embryonic development, and may also be operative in other malformations. Thus the striking similarity in morphology between the nuchal hygromata in some fetuses and the cystic hygromata as observed in children (more rarely in adults) strongly suggests that the latter may develop as the result of a localized obstruction during an early developmental phase. From lymphangiographic and histopathological observations one may conclude that the same mechanism probably underlies primary lymphedema (Cough, 1966), lymphangiectasia pulmonalis (Laurence, 1955, 1959) and lymphangiectasia intestinalis (Pomerantz and Waldman, 1963). In all these conditions the ultimate form of the malformations may well be determined by the severity of impairment of lymph flow and the time of its onset.

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