View points

Lymph System Dysplasias: Semantic Analysis

Papendieck.CM*, Barbosa ML*, Pozo P**, Braun D***, Bajaroff K****, Dell´Oro V***, Wydler V.*****

Angiopediatria–Buenos Aires–Argentina

Abstract **Background and aims:** As surgical treatment evolves and local control has improved, the failure of cancer treatment has largely remained the result of systemic metastasis. Identification of patients most likely to benefit from adjuvant strategies remains problematic. In order to develop a new standard of curative effect, this study was designed to track the number of CTCs in patients with lung cancer during chemotherapy. **Methods:** Samples of peripheral blood was taken from each lung cancer patients (n=32) on the day before chemotherapy as well as the third week after the chemotherapy cycle. The samples were subjected to real-time fqRT-PCR. Meanwhile the tumour size was determined by chest X-ray or computed tomograghy. **Results:** Compared to that of pre-chemotherapy, the expression level of CK19 in the patients significantly declined after chemotherapy (t=4.659, P=0.000). The level of CK19 mRNA in patients with SCLC was higher than that of patients with NSCLC (t=1.944, P=0.061). The change of CK19 mRNA correlated well with the type during the treatment. Relatively the shift of SCLC is more obvious (t=6.073, P=0.000). The variation of CK19 mRNA before and after chemotherapy was positively related to the disparity of tumour burden (r=0.593). There was also a significant association between the type (NSCLC vs. SCLC) and the change of tumour size (t=3.686, P=0.001).The positive rate before chemotherapy was 71.9% (23/32), while that after chemotherapy was 37.5% (12/32), indicating that 11 patients converted into negative after chemotherapy. Of the 16 patients which were in Ⅳ-stage, 11 cases were positive (11/16,68.8%). Surprisingly, of the remaining 16 patients which were Ⅱ/Ⅲ stage, 12 cases were regarded as positive according to the criteria (12/6,75%). **Conclusions:** The real-time fluorescent quantitative-PCR approach is useful for measuring the relative number of CTCs in a patients' peripheral blood to monitor the effectiveness of treatment, and for designing more comprehensive and reasonable therapeutic regimes at earlier dates for patients. The treatment response can be immediately assessed by serial quantitation of CTCs after chemotherapy, and therefore this method highlights an alternative approach to rapidly access the patient's response to treatment.

The dialogue about malformations of the lymphatic system, is not frequent. Being the lymphatic system multi structural, because of multi function – few times it is considered as a whole (1): the lymph vessels, in all their kinds, the lymph nodes, a third part of the spleen, the Peyer plaques, a part of the bone marrow, the tonsils in general and the thymus gland. The dysplasias where grouped by E.Malan [1], analysed by JB.Mulliken[2], systematized by ISSVA- into trunkular and extratrunkular malformations [3]. Since 1990, with similar purposes, we have classified them into LAD I, Lymph angio dysplasias, and LAD II, lymph adeno (nodal) dysplasias, being both aspects, essential in the dynamics – transit and distribution- of the lymph [4] . The rest of the specific extra trunkular structures, are analysed in a different context, mainly from a functional point of view, as pathologies and specific syndromes.

The semantic of the dysplasias is of particular interest, as well as, the analysis of their interpretation, as the cause of a primary dysfunction, in pediatrics, and theire expression as syndromes.

The Lymphatic System, is a set of three vascular hemi circuits, between the virtual interstitial spaces, and the venous system -and a set of two types of organs, primary and secondary-the lymph nodes (400 -700), the spleen (1/3), a part of the bone marrow, the tonsils, the Peyer plaques, and the thy mus gland-inserted the first, and linked the second with the canalicular structures. In this way, the lymphatic system is multi structural, and in consequence, multi functional[5]. The three vascular hemi circuits of the system, are the right great lymhatic vein (ductus lymphaticus dexter), the network of the chyle, and the confluence of the thoracic duct in the left jugulo suclavia venous junction, with systemic lymph and the chylus. The Pecquet-Cisterna chyli-and the thoracic duct, are the most specific segment of mixed lymph transit.

One of the functions of the canalicular-system, is to recognize and rescue, from the virtual interstitial spaces the part of liquids linked to specific hight weigth molecular components, like proteins, that composed the lymph fluid in its first stage, which needs the transit in the lymph vessels net.

The canalicular system begins with the initial lymphatics [6], pre and capillary, where they lack basal membrane. Embriologically, they share their origin with the venous endothelium. The inserted nodal network, is a specific segment, where the lymph concentrates, due to the transference of water to the venous system (0

*CMPapendieck. MD. Prof. Pediatric Surgeon
*ML Barbosa.MD Pediatric Surgeon
**P Pozo MD Pediatric anesthesiolgy
***D.Braun Pediatric.Physical Therapy
***V.Dell'Oro. Physical Therapy
****K Bajaroff Nutritionyst
*****V Wydler Psycologyst
http:/www.angiopediatria
Arenales 3605 PB 1, CP 1425 Buenos Aires, Argentina
ISSN: 1538-5124/$ - see front matter

-10cc /day / per node) and the foreign elements are identified and cytoquines and leucocytes are added. The lymph does not contain erythrocyte and Fe, therefore there is no function of transporting of O_2. The Lymph system is uni direccional, because of its valvulation, and is functionally autonomous under the stimulus of the demand and offer of lymph, through its functional units, the lymphangions. All the tissues, so all cells, produce components of lymph; lymph is one of the results of its work. There are as many lymphs as kind of tissues, but basically two, the systemic lymph and the quality chyle.

Each one of the lymph systsem segments, may be malformed-the canalicular network and the different kinds of linked organs. A malformation, is a dysplasia [7] . The dysplasias of the lymph system-may be structural or of the design of the system. As concrete examples, a trunkular avalvulation, and a agenesia of the thoracic duct.

An agenesia is in general replaced functionally by another circuit, in a different anatomical place. In this sense, an agenesia is not a dysplasia in itself- what not is, can not be; but it is abnormal, a dysplasia in the design of the system. An in-between situation: the hipoplasias. As long as there are fewer, it is simply a hypoplasia, if its structure is normal, But it surely expresses dysfunction – e.g. the lymph capillalry hypoplasia in the Nonne-Milroys disease [8], Milroy or Meige Syndrome[9] with primary lymphedema.

To have a parallel with the semantic of the arterio-venous dysplasias, the lymph system dysplasias are classified in the same sense: Trunkular and extra trunkular. The lymph system, has, wih both aspects, an important expression on the combined angiodysplasic syndromes[10]

The lymph nodes, inserted in the canalicular net, are in this way directly linked to the hemi circuit, as a necessary segment. But they are indeed different organs, because of their structures and functions. This justifies to analize the dysplasias of the canalicular and nodal system in two steps[11].

It is useful to simplify the semantic aspects, but sometimes it is dificult to respect the terminology-e.g. the lymphangion, the functional unit of the vessels, the lymphangioma, structurally a lymphatic aneurysm of one or more lymphangions, and lymphangiomatosis-a microcystic capillary aneurismatic malformation of the lymph system. Lymphangioma and cystic hygroma, means the same. The functional unit . lymphangion, the cystic malformation, lymphangioma. The cystic hygroma, deserves tha analysis of the term: hygro-means H_2O, moisture, and oma, tumor. Lymph is not only H_2O, and least of all, chylus. There are posible different cystic hygromas in the body. Both terms, lymphangioma and hygroma, have the suffix oma-biologycally tumor, but here, lymphangio dysplasic tumor. Lymphangiomatosis , is the multiple. There are no a rigth word to define it in an another way. Also includes the lymphangioma circunscriptum (hygroma circunscriptum?) but it is really not circunscribed, as it is a intradermic and or more, multi cystic hygroma or lymphangiomatosis. Lymphangioma is therefore a paralel to the venous and arterial congenital aneurysm. Lymphangiomatosis is a paralel to phleboangiomatosis – superficial or deep venous malformation,(segmentary, hemicorporeal, uni or bilateral), and hemangiomatosis. Tosis means multiplicity (paralel to others: e.g. neurofibromatosis).

The biological classification of vascular tumors (12) must be respected, wich reflects an important meaning by consensus, in the interpretation of these pathologies. But the words angiodysplasic tumor, are interesting or necessary.

The cystic hygroma-lymphangioma-can be mixed. One part hemangioma, tumor, and or a superficial or deep veneous malformation, and the cystic lymphatic component-in extensió n-a hemolymphangioma, tumor + angiodysplasic tumor. These considerations are important for the posible treatments. A malformation is a life scheme: a tumor, develops according to its structure. There will be different points of view, to classify despite similar intentions.

Trunkular dysplasias of the lymph system, may be identified by: a direct lymphography, with LUF, the best study, but not easily accesible; a MRI, together with a direct lymphography or Gadobutrol; a lymphochromy with PBV; a radioisotopic lymphography, and at last, but not least, an anatomo- pathologycal study.

LAD I: 1. Disvalvulation

2. Avalvulation

3. Lymphangioleiomyomatosis

4. Neurovegetative anomaly. Functionally a lymphangio neurosis.

5. Hipoplasia, in n? and calibre.

6. Lymphangiectasia

7. Lymphangioma

8. Lymphangiomatosis

Every lymph system dysplasia that means or leads to hypertension of the circuit, can be expressed as primary lymphedema. Primary lymphedema is therefore a edema, generated by a intrinsic dysplasia of the lymph system, and, or, a functional interstitial dysturbance on the endothelium of the initial lymphatics [13] .

It is rare to find together a lymphangioma, with primary lymphedema. The same is frequent with a lymphangiomatosis – similar as all the valvular dysplasias, unless they develop as internal or external fistula. It is frequent to observe this situation in the Turner and Noonan syndrome. Also, after hormonal treatments, in the same syndromes, as secondary pathology.

Valvular dysplasias leads to lymphangiectasias, with fistulas and lymphedema.

Malformations of he lymph vessel valves, means also lymphatic reflux with all its significances, in particular, with chyle.

Lymphangiomas are posible in all the organs. Also in the bone. Eg. the bone disappearing syndrome or phantom bone disease (Gorham Stout syndrome)[14], associated with chylus reflux and hemangiomas (Haferkamp syndrome) sometime important lymphangiomas exist in the space of the original lymphatic sinuses. The embriology can explain the localizations, and the associated malformations of the lymph system.

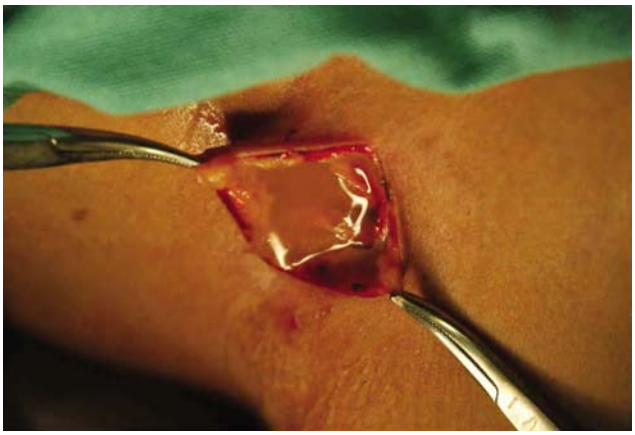

Fig.1.Inguinal mixed lymph reflux, during a micro inguinal (2cm) surgical vascular acces

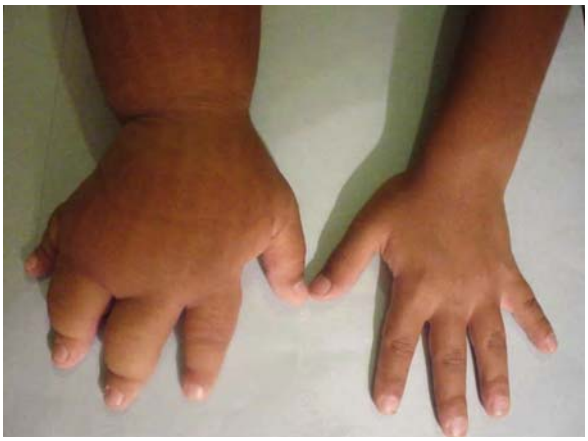

Fig.2.Primary lymphedema of the left hand and in general, upper limb, grade II

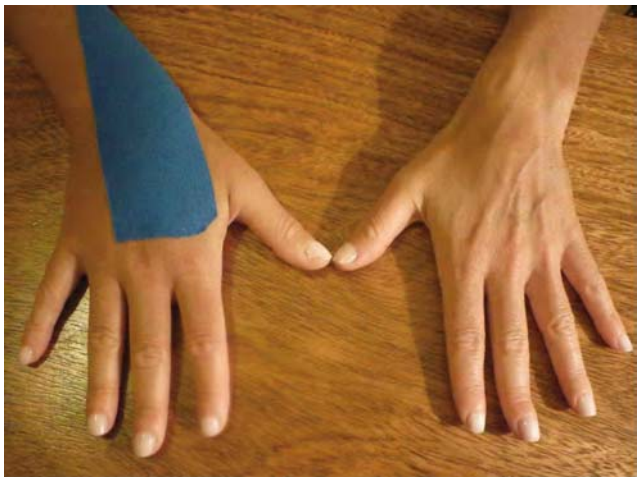

Fig.3. Primary lymphedema of the right hand, grade 0 to I, with taping.

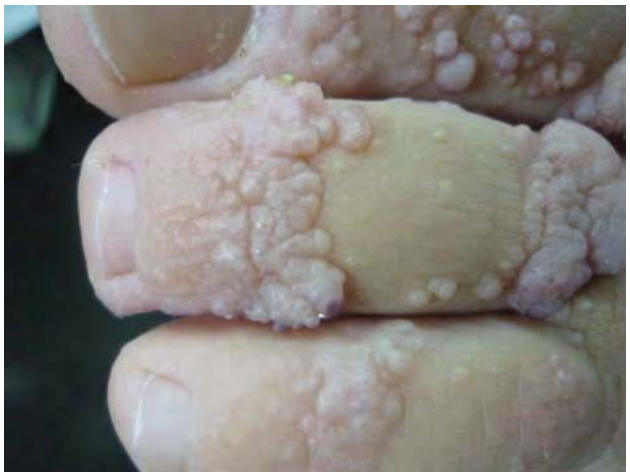

Fig.4.Primary lymphedema of the left foot, with verrucosis on the toes because chylus Reflux.

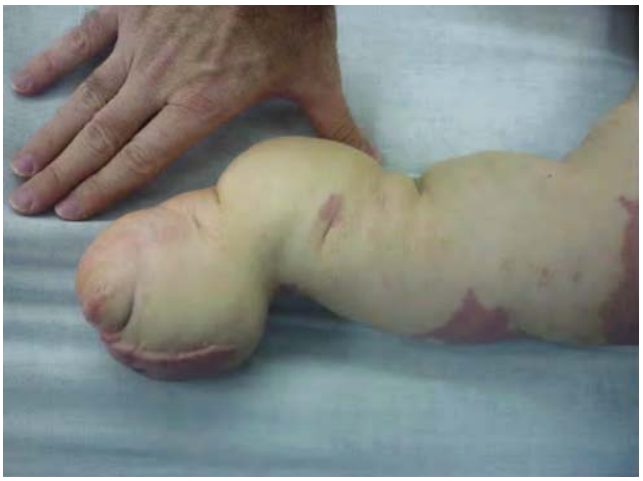

Fig.5. Primary Lmphedema on a Klippel Trenaunay Servelle Syndrome in a baby.Lower Limb. Varicous osteo hypertrophy and hemangiomatosis and deep venous dysplasia

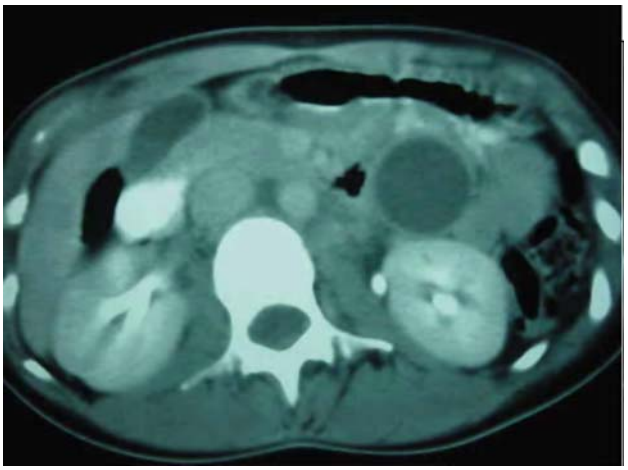

Fig.6.Prerenal retroperitoneal Lymphangioma

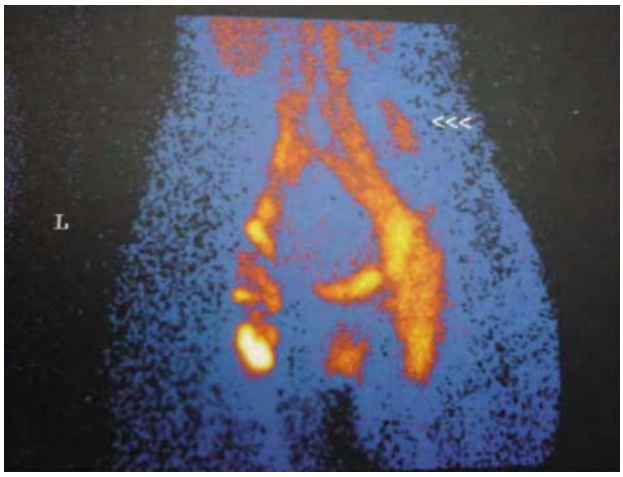

Fig.7. Radioisotopic lymphography with iliac and inguinal reflux and a left paravertebral Collection.

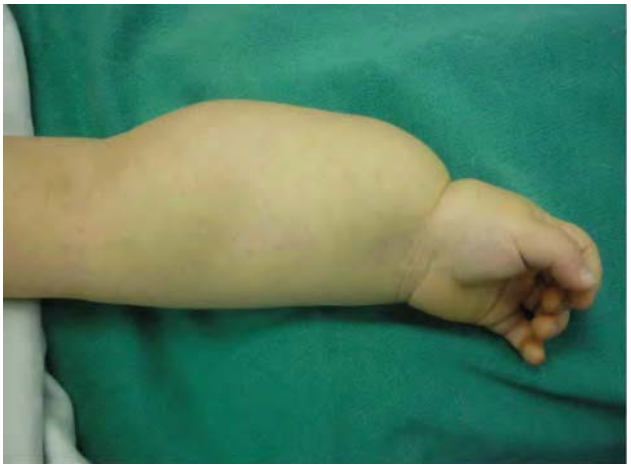

Fig.8.Subcutaneous lymphangiomatosis in the forearm of a baby.

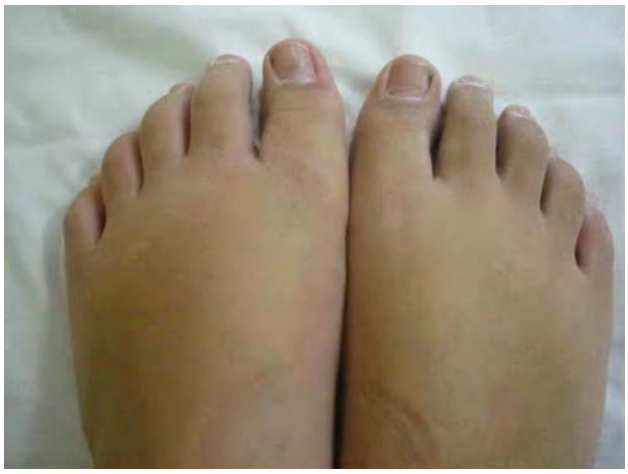

Fig.9. Primary lymphedema with lymphangiomatosis

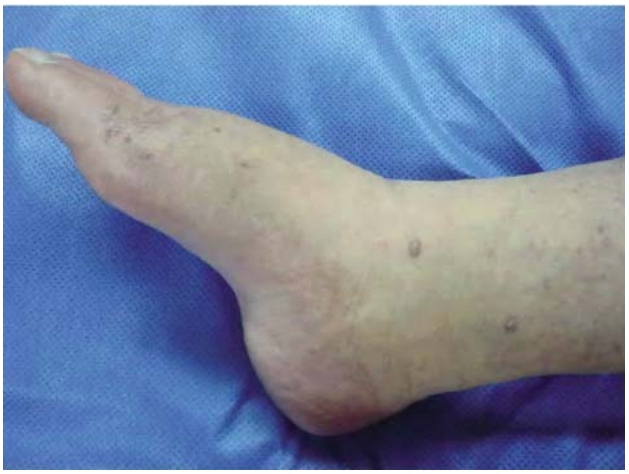

Fig.10. Lymphangiomatosis and trans epidermal lymph reflux

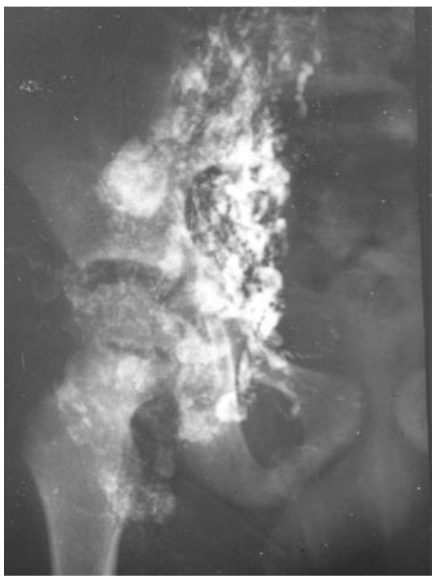

Fig.11. Direct lymphography with a important inguinal nodal dysfunction.

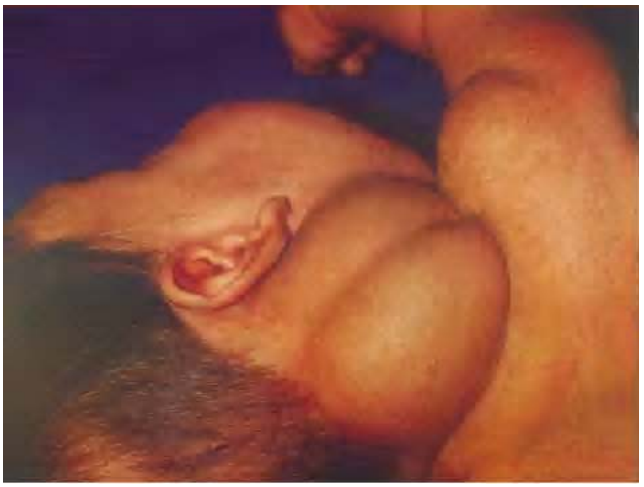

Fig.12. Cervical lymphangioma

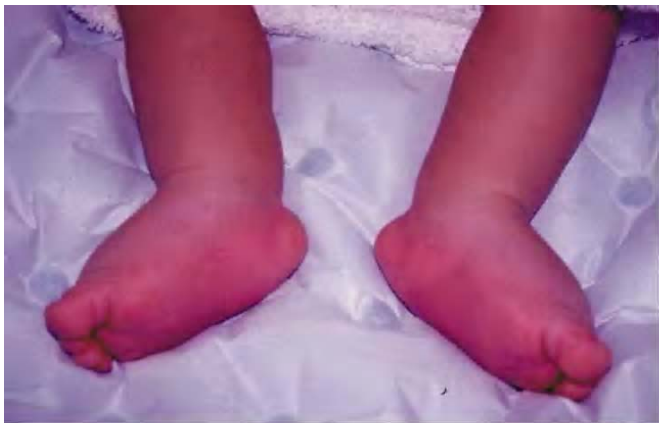

Fig.13. Primay lymphedema of the feet, in a baby.

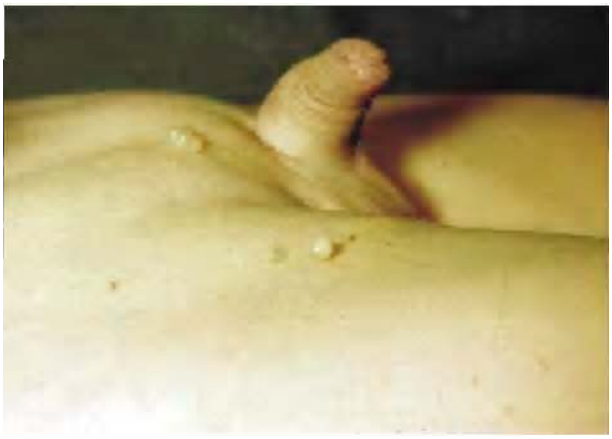

Fig.14. Lymph reflux in the inguino genital areas, in a Noonan syndrome.

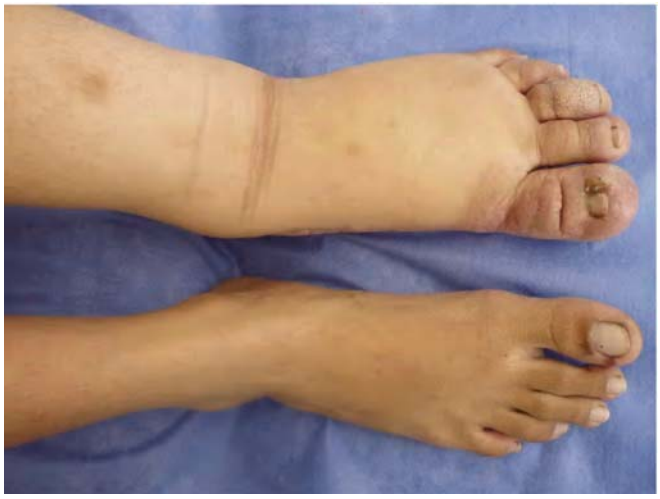

Fig.15. Lymphangiomatosis, Primary Lymphedema and Verrucoris.

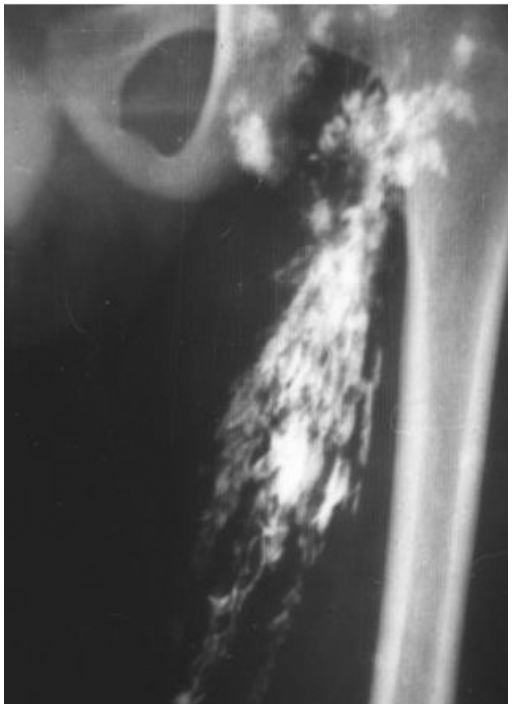

Fig.16. Lymph transit blockade on inguinal node level. Direct Lymphography.

Canalicular or trunkular hyperplasia, in numbers, is complex to understand in its primary character. It can be seen in Great Angiodysplasic Syndromes, or Combined (BAS)[15-16]with reflux and in a part of primary lymphedemas.. There exists primary lymphedema with hypo, normal or hyperplasia of lymph vessels, dilated or not, with nodal dysplasias. (LAAD- lymph angio adeno-nodal- dysplasias)

Acquired dysplasias are posible: e.g.the post surgical or traumatic lymphocele: endothelized, a lymphangioma : induced increase of growth, and lymphangiectasias because of valvular incompetence.

We have called the nodal dysplasias, lymph adeno dysplasias (LAD II) The term adeno may generate discrepancy.. The node is not a gland. Adeno means this; however, in medicine, the terms adenitis, lymphadenitis, among others, is used, with consensus.

Dysplasias of the nodal level:

1. Hypoplasia
2. Angiomatosis (e.g. intra nodal hemangioma or lymphangioma)
3. Lymphangiomatosis
4. Capsular or cortical fibrosis
5. Central fibrosis
6. Global fibrosis.
7. LAD I dysplasias.

Possibly in primary lymphedemas, the most frequent cause of dysplasia, is the congenital nodal fibrosis, progressive or not, with no clear origin.

For medicine base on evidence, to achieve these diagnosis, it is necessary a nodal micro biopsy, which includes all the structures of the node. To have it, a lateral and external sample is necessary, to avoid sagital and transversal, internodal circuits.

The lymph system dysplasias are the most frequent (% is unknown) causes of primary lymphedema. Also in combined syndromes[17-18].

The chylus circuit, can have the same dysplasias, with the addition of its particular origin in the subepitelial small intestine level, the chylus vessels, the two retro peritoneal trunks to the Pecquet cistern. The primary chyloperitoneum and pleural outflow or efusion of chyle, responds to a trunkular anomaly of the chyle collectors [19]. The lack of its confluence, means aberrant paths. In this way, also a chylartrosis or to other cavities or organs, and cutaneo mucosal levels, is explained by chylus reflux, known as verrucosis in the skin. Chyluria, or exudative enteropathy. The thoracic duct can have its confluence to que jugulosuclavia level, left (90%)or right (10%) , that is normal. This does not mean, that the lymphvein, changes its side. They are anomalies of the system, and not of their structures .The thoracic duct can be double or primarily agenetic, replaced by paravertebral ducts or on the chest wall to the axilary vein. Sometimes, this appears in combined syndromes, e.g. the Proteus syndrome [20], the Klippel Trenaunay Servelle syndrome [21]and other BAS [22]. Common aspect in them, is the trunkular, or deep venous hypertension, comming back to the reflection on the embriogenesis of the veno-lymphatic system.

Comment

The malformations, dysplasias, of the lymph system, mainly congenital, in pediatrics, are an important chapter in lymphology [23].

Important because its significance as malformations, as life time pathologies, with considerable physical and psycho-social aspects, and not at least, considerations about the significance, of the lymph system hypertensió n during a life. A clasiffication is helpfull for its understanding, and the terminology makes some posible in considerations about theirs therapeutical aspects. There is no consensus in some treatments, or attemps for new therapeutical approaches. Through sumarized aspects, it is intention to reveal and disclose some points.

References

1. Malan E: Vascular Malformations. Angiodysplasias. Milano. 1974. C.Erba F.
2. Mulliken JB, Young: Vascular Birthmarks: Haemangiomas and Malformations. 1988. WB Saunders. Philadelphia.
3. Loose AD, Weber J. Angeborene Gefaessmissbildungen.Angiodysplasien1997. Perriodica Angiologica Nº21: Belov St.Geschichte. Epidemiologie und Klassifikation Angeborener Gefassfehler: 17-23.
4. Barbosa ML, Papendieck CM: Linfangioadenodisplasias en pediatria. 2000. Patologia Vascular . Madrid.: 6: 323-7
5. Foldi M, Foldi E.Kubik S: Lehrbuch der Lymphologie.6 Ed. 2005. Elsevier.
6. Olszewski W: Lymphstasis pathophysiology, diagnosis and treatment. 2001 CRC Press, Inc. Florida
7. Thomaz JB, Belczack CRQ. 2006 Rd, Rubio, Tratado de Flebologia e Linfologia Chap.65. Angiodisplasias em Pediatria.Linfedema angiodisplasico.:767-85
8. Foldi M, Foldi E, Kubik S. Textbook of Lymphology 2003 5Ed. Elsevier
9. Milroy WF: An undescribed variety of lymphedema.NY Med J 1892.59:505-8
10. Simkin R: Tratado de Patologia Venosa y Linfatica. 2008. Ed. Medrano. Buenos Aires: Sí ndromes Angiodisplasicos en Pediatria.Chap. 41:851-75
11. Papendieck CM :Linfedema en Pediatria. Clasificacion yetiopatogenia. 2003 Rev Hosp Ninos BAires. 45:13-22
12. Mulliken JB, Glowacki J: Haemangiomas and vascular malformations in infants and children: a clasiffication based on endothelial charactesistics. Plast.Reconst. Surg. 1982; 59: 412-20
13. International Consensus. Best Practise for the Management of Lymphedema. MEP 2006. Thames Valley University. London.Centre for research and impementation of Clinical Practice.
14. Gorham W, Stout AP: Massive osteolysis. Phantom bone. J Bone Joint Surg.1955; 37 A:985-1004.
15. Papendieck CM: Angiodyslasias in Pediatrics.Atlas color.1988. Editorial Medica Panamerican. Buenos Aires.
16. Papendieck CM. Pediatric Angiology Subjects. Atlas color. 1992. Editorial Medica Panamericana.Buenos Aires
17. Hennekam RC. Syndromic Lymphatic Maldevelopment 4th Internat. Conferemce National Lymphedema Network- Florida. 2000 Abstracts:11-12.
18. Witte HM, Bernas M, Northrup K, Witte Ch.: Molecular Lymphology and Genetics of lymphedema-Angiodysplasia Syndromes. Textbook of Lymphology. Foldi M, Foldi E, Kubik S: 2003. 1th Ed. Elsevier.
19. Servelle M, Nogez C: The chyliferous vessels.1981. Expansion Scientifique Franc.
20. Wiedeman HR: The Proteus Syndrome. 1983 Eur J Pediatr. 140:145.
21. Papendieck CM. Barbosa ML, Pozo P, Braun D: Klippel Trenaunay Servelle Syndrome. 2003. Lymphaticc Research and Boiogy 1:81-5
22. Papendieck CM The Big Angiodisplasic Syndromes in pediatrics with the participation of the lymphatic system. 1998. Progress in Lymphology XVI.31 (suppl) 390-2.
23. The Diagnosis and Treatment of Peripheral Lymphedema. Consensus Document of The Internacional Society of Lymphology(ISL) Lymphology.1995;36:84-91.