VL-DUAL EDITORIAL

Lymphatic Research in the Future

'Age of onset'-based classification of Primary Lymphedema: Controversy to lead Lymphatic Research

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Primary lymphedema is one of chronic lymphedemas with clinical condition of diffuse swelling of affected limb/region as the result of a less-than-optimal transport capacity of the lymphatic system as the result of the blockage of lymph-transport/collection; it generally progresses more slowly than secondary lymphedema, often clinically presenting later[1-4].

True incidence and prevalence are largely unknown due to under-reporting and under-recognition but much more common, over 90% of cases among the pediatric population.Because, primary lymphedema represents the outcome of defective development so that it already exists at birth as 'inborn' abnormalities, often associated with various genetic syndromes or can be idiopathic[5-8].

Indeed, primary lymphedema is the most common lymphatic dysplasia among the lymphatic malformations as the outcome of defective development from the 'later' stage of lymphangiogenesis, classified to 'truncular' lesions, based on direct involvement to the matured lymphatic vessels/nodes in various extents of defective condition.Therefore, it is clinically manifested as a macroscopically irregular or abnormal structural development in general[9-12].

Hence, primary lymphedema represents mainly a clinical condition of truncular malformations of the lymphatic system with lymphatic truncular hypoplasia (89%), aplasia, numerical hyperplasia, or dilation (lymphangiectasia-10%) with valvular incompetence although some primary lymphedemas have very little structural derangement and represent only a functional defect to require detection in molecular or other functional terms that is molecular in origin[13-16].

Regardless, primary lymphedemas have been classified into three groups depending on the age of onset: Congenital (before age 2), Praecox (between age 2 and 25) and Tarda (after age 35).But there is much doubt in this conventional classification/concept classifying all lymphedema solely on the basis of the age of the onset: congenital, praecox and tarda as one spectrum of the disease[17-20].

As a matter of fact, congenital type of primary lymphedema is frequently associated with other malformations (heart, mental, renal, etc.) while praecox and tarda never show these features.Besides, Tarda is bilateral in most patients BUT bilateral involvement occurs in only 30% of patients with praecox, even though 70% of praecox patients have bilateral anomalies to start with.This is likely due to mosaicism where a patient may clinically have only unilateral clinical symptoms with underlying bilateral pathology[21-24].

Lymphedema-distichiasis syndrome, one of autosomal-dominant syndromes, for example, caused by mutations in the FOXC2 gene, associated with congenital distichiasis (extra eyelashes arising from the Meibomian gland) (95%) and congenital heart disease (8%), never manifests lymphedema at birth, although it should be present at birth by definition as true malformations.

But the lymphedema usually presents in late childhood or puberty among lymphedema-distichiasis syndrome and may be delayed until the 5th decade[25-28].

Therefore, terms like tarda and precox are outdated terms, potentially misleading as sole criteria for classification.Indeed, there is some objection to classifying all lymphedema on the basis of the conventional spectrum based on the age of the onset. The arbitrary age of 35 used to separate 'tarda' from 'precox' is not clinically useful because this classification does not imply a mechanism or pathogenesis[3, 4].

Indeed, the cause of decreased lymphatic transport among primary lymphedema can be an intrinsic 'defect' or a 'malfunction' of the lymph conducting elements.Hence, primary lymphedema includes all those manifestations of lymphedema that represent an inherited condition although there is some controversy whether all lymphedema and lymphatic malformations are genetically derived or not[29-32].

Primary lymphedema is now generally considered as the outcome of a genetically determined abnormality of lymphatic anatomy or function caused by abnormal (mutant) genes.Hence, clinical research on the lymphedema ought to review on this 'age of onset'-based classic concept/classification of primary lymphedema and should accommodate a new concept on the primary lymphedema based on the genetic aspect accordingly[32-36].

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