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CONGENITAL LYMPHATIC DYSPLASIAS: GENETICS REVIEW AND RESOURCES FOR THE LYMPHOLOGIST

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ABSTRACT

Diagnosing congenital lymphatic dysplasia and counseling the parents of babies with possible genetic conditions represents a difficult task. This article attempts to provide a guide to establishing genetic tools and a reference library for use in the diagnostic work-up of congenital lymphatic diseases. The tools that are outlined herein are not meant to replace genetic counseling; their role is merely to facilitate the interaction between lymphologist and geneticist. These tools are a way of identifying lymphatic dysplasias at a very early stage.

Keywords: congenital lymphatic dysplasia, genetic tool, books, websites, genetic resources

Lymphedema, the swelling resulting from impaired drainage of fluid out of the body's tissues, is classified as either a primary or secondary form (1). Primary lymphedema is usually considered the result of an inherited abnormality of the lymphatic system, but the cause is clearly defined only in a very small number of patients. Secondary lymphedema is the result of a damaged or blocked lymphatic system usually caused by surgery, radiotherapy, traumatic injury, or infection. In the Western world, lymphedema is most often observed following breast cancer radiation and surgical therapy. It has been estimated that there are more than 200 million cases of lymphedema worldwide, with filariasis being the most common cause.

Primary lymphedema has been estimated to occur in about one in six thousand individuals with higher frequency in females than in males. Time of onset varies. Primary lymphedema can be present from birth (congenital lymphedema), symptoms can begin at puberty (lymphedema praecox), or onset may occur in adulthood (lymphedema tarda) (2).

In a recent article, Northup et al (3) reviewed the syndromic classification of hereditary lymphedema. Congenital lymphatic dysplasia may be present at birth with various degrees of clinical severity, spanning from nonimmune hydrops fetalis possibly complicated by chylothorax and respiratory distress, by chylopericardium or chylous ascites, to mild degrees of peripheral limb lymphedema. Primary (idiopathic) lymphedema syndromes, congenital chylothorax, and idiopathic effusions (often chylous) may be encompassed by the term "lymphatic dysplasia syndrome." Recently, both pediatricians and neonatologists have been involved in the study and in the treatment of lymphatic dysplasia due to more careful attention to the early onset of lymphedema. Diagnosing congenital lymphatic dysplasias and counselling the parents of affected babies can be a difficult task. In this article we report on the tools which, in our opinion, are most

often useful in pediatric and neonatal units (i.e., textbooks, databases and websites) to assist lymphologists in identifying babies with subtle lymphatic features as well as babies who present severe lymphatic impairment. We do not imply that the tools outlined here could replace the genetic and/or lymphologic consultation(s), but rather these tools can serve to identify lymphatic dysplasias at a very early stage.

BOOKS

Syndromes of the Head and Neck (4). This text may be considered the definitive work on dysmorphology, covering most genetic syndromes that affect body structure. Molecular genetics aspects of malformation disorders are extensively reviewed. The 5th Edition is scheduled for March 2009.

Smith's Recognizable Patterns of Human Malformation (5). This "classic" and well known book represents an important source for guidance on diagnosis, prognosis, plan management, and genetic counseling. It focuses on the patterns of human defects caused by inborn errors in morphogenesis as opposed to defects caused by mechanical problems. It provides a wealth of information on normal and abnormal morphogenesis, clinical approaches to specific diagnoses, and normal standards of measurement for the entire spectrum of disorders.

Catalogue of Unbalanced Chromosome Aberrations in Man (6) describes the phenotypes associated with the great majority of cytogenetically visible unbalanced chromosome abnormalities. This book presents a comprehensive and updated catalogue of the already large, and rapidly growing number of chromosome aberrations in man. The catalogue is an important aid to any clinician treating patients with autosomal chromosome aberrations as well as to physicians and biologists working in cytogenic laboratories and human genetic institutes.

Management of Genetic Syndromes (7) offers a realistic approach to what parents and physicians can expect from infancy to adulthood, as well as whether there is any risk of recurrence of the condition in the affected individual's siblings and offspring, whether prenatal diagnosis is available, and the spectrum of variation that may occur.

GENETIC DATABASES

London Medical Database (LMD) (http://www.lmdatabases.com/). In 2003, publication of the Oxford Medical Databases was taken over by London Medical Databases Ltd, a company owned by the authors and original publishers of the Oxford Medical Databases. LMD produces databases in the medical genetics field. Currently the LMD series comprises:

Winter-Baraitser Dysmorphology Database (WBDD), Baraitser-Winter Neurogenetics Database (BWDB), and London Ophthalmic Genetics Database (GENEEYE). The WBDD currently contains information on nearly 4,000 dysmorphic, multiple congenital anomaly and mental retardation syndromes. It includes single gene disorders, sporadic conditions, and those caused by environmental agents. Although WBDD mainly contains information about non-chromosomal multiple congenital anomaly syndromes, it also includes information about distinctive microdeletion syndromes and those resulting from uniparental disomy. WBDD contains nearly 41,000 fully searchable references, linked to the appropriate syndromes.

The BWND currently contains information on over 3,700 syndromes involving the central and peripheral nervous system seen in adults and children. Like the WBDD, it contains information on single gene disorders, sporadic conditions, and those caused by some environmental agents. In BWND, search facilities are enhanced by the ability to use age at onset of neurological features, neurological and other clinical features, neuroradiological findings, changes

seen on electrophysiological investigation, abnormal biochemistry, and neuropathological findings. BWND contains approximately 44,000 fully searchable references, linked to the appropriate syndromes.

The Photo Library. Now integrated into WBDD and BWND, the Photo Library is a superb collection of 17,500 photographs that show the main dysmorphic features of the syndrome and other relevant images, such as skeletal radiographs, hair, microscopy, etc. In the case of neurogenetic syndromes, there are CT and MRI images showing their characteristic neuroradiological features, examples of EEG changes or the changes observed on other key electrophysiological investigations and, where relevant, pictures of the characteristic neuropathology, including nerve and muscle biopsy.

The latest addition to the LMD series, GENEEYE is a comprehensive database of over 2,500 genetic ophthalmic conditions. Ophthalmologic features have been considerably extended and all the syndromes from WBDD and BWND that involve eye features have been extracted and reclassified according to their features. Several single congenital anomalies, both genetic and sporadic, have also been added, including all the corneal dystrophies, macular dystrophies, the scores of different rod-cone dystrophies and much else. GENEEYE contains over 34,000 fully searchable references, linked to the appropriate syndromes.

POSSUM Database (http://www.possum.net.au/) contains information on more than 3,000 syndromes, including multiple malformation chromosomal and metabolic conditions and skeletal dysplasias. The comprehensive mediabase includes x-rays, diagrams, and histopathology slides. Syndrome commentaries provide detailed information about clinical attributes, differential diagnoses, radiology and genetics. It is continuously updated, and data are uploaded every two months. In the past two years POSSUM has been re-developed as a web-based program – POSSUM Web – a database of multiple malformations, metabolic, teratogenic, chromosomal and skeletal syndromes and their images – to be used for teaching/learning and diagnosis. POSSUM is linked to OMIM (Online Mendelian Inheritance in Man).

The Human Cytogenetics Database, Albert Schinzel (http://www.oup.co.uk/) was developed as a tool for the clinical diagnosis of autosomal chromosome aberrations. It arose from the need to obtain information quickly on the many rare cytogenetic aberrations. The system is very much based on clinical practice and experience. Clinical findings on phenotype, development, and fate of the affected patients are specific tools. The database contains information on more than 1,000 autosomal chromosome aberrations.

SynDiag (Syndrome Diagnosis) Database (http://members.tripod.com/~kolosov/) contains more than 2,600 carefully clinically described nosologic forms of MCA/MR syndromes of different etiology, skeletal dysplasias, ectodermal dysplasias, and some systemic anomalies. Adding the reference book of phenotypic sign library (more than 1,500 signs) and of pathological gene localization and molecular defects will improve the database.

Jablonski's Multiple Congenital Anomaly/Mental Retardation (MCA/MR) Syndromes Database (http://www.nlm.nih.gov/archive//20061212/mesh/jablonski/syndrome_db.html) describes syndromes in which multiple congenital anomalies are associated with mental retardation and consists of structured descriptions of approximately 700 of the 1,600-2,000 syndromes involving congenital abnormalities known to be associated with mental retardation. It was made available in 1999; however, it has not been maintained or updated, nor is it expected that the data will be updated. Since the data have not been updated, the

information may now be obsolete and not reflect current medical knowledge.

NeurometPLUS (Neurometabolic Disorders and Other Hereditary Neuropediatric Diseases (http://lemarpublishers.com/neuromet.html) Neurometabolic Conditions and other Hereditary Neuropediatric Diseases Database. An "easy to use" database on neurometabolic disorders and other neuropediatric diseases. At present, NeurometPlus is not available for purchase through the Internet. Future plans include a downloadable version via this website.

WEBSITES

Online Mendelian Inheritance in Man OMIM (www.ncbi.nlm.nih.gov/). OMIM refers to all known mendelian disorders and over 12,000 genes, focusing on the relationship between phenotype and genotype. It is updated daily, and the entries contain copious links to other genetics resources. Entries include general description, phenotype, clinical features, biochemistry, and genotype, mode of inheritance, diagnosis, management, molecular genetics, references, clinical synopsis, pictures, and date edited. Twelve book editions of Mendelian Inheritance in Man (MIM) (1966-1998) have been published. The online version OMIM was created in 1985, and became available on the internet in 1987. In 1995, OMIM was developed for the World Wide Web by NCBI, the National Center for Biotechnology Information.

PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) is a free search engine for accessing the MEDLINE database of citations and abstracts of biomedical research articles. It is offered by the United States National Library of Medicine at the National Institutes of Health as part of the Entrez information retrieval system, together with OMIM. PubMed search engine is probably the most used method to retrieve biomedical literature and is very useful when you are searching for a specific query. It may be less informative if you need a search starting from non-specific signs or symptoms, as usually occurs when approaching patients with undiagnosed syndromic characteristics.

Clinical Genetics Computer Resources (http://www.kumc.edu/gec/prof/genecomp) provides a great deal of information on Diagnostic Programs, Pedigree Drawing, Teratogens, Other Sites, Databases, Education, Internet Health References, and Genetic Conditions.
Genetic Tools (http://www.genetests.org/servlet/access?id=INSERTID&key=INSERTKEY&fcn=y&filename=/tools/index.html). This site includes several sections; Genetics Concepts and Skills, Teaching Cases, Ethical, Legal, Social, and Cultural Issues, and links to other resources, to facilitate teaching about genetics in primary care settings.

Computational Molecular Biology at NIH (http://molbio.info.nih.gov/db.html) provides, among others items, Databases for molecular biology, Molecular Biology Desk Reference with a collection of basic information, and Other Molecular Biology Resources providing major websites for molecular biology.

Chromosomal Variation in Man: A Catalog of Chromosomal Variants and Anomalies (http://www.wiley.com/legacy/products/subject/life/borgaonkar/). Access to the database is open to the public and freely available. This database provides an unparalleled means of reviewing the world literature on all common and rare chromosomal alterations and abnormalities. Organized for easy access, coverage is divided into three main subject areas: variations and anomalies, numerical anomalies, and chromosomal breakage syndromes. It includes new banding techniques, spectral karyotyping of chromosome, FISH, UPD, and PRINS. The database documents information on the

availability of mutant cell lines and presents chromosome alterations with a list that cross-references band numbers. It contains over 24,000 entries that have been continuously up-dated since 1974.

GeneTests (http://www.geneclinics.org/) is a publicly funded medical genetics information resource developed for physicians, other healthcare providers, and researchers, available at no cost to all interested persons. The site provides various resources. GeneReviews (Online publication of expert-authored disease reviews); Laboratory Directory (International directory of genetic testing laboratories); Clinic Directory (International directory of genetics and prenatal diagnosis clinics); Educational Materials (Illustrated glossary, genetic services, PowerPoint® slide presentations).

GENINFER (http://groups.csail.mit.edu/medg/projects/geninfer.html) is a computer program that can be used to assist genetic counselors when evaluating the risk of recurrence of genetic disorders based on the analysis of family pedigrees.

ORPHANET (http://www.orpha.net/) is the portal for rare diseases and orphan drugs. The main menu of this website comprises: Rare diseases, Orphan drugs, Clinical Diagnostic tests, Research and trials, Patient's organizations, Directory of resources, and Education and media.

CHID (Combined Health Information Database) (http://198.232.252.23/). Effective September 1, 2006, the Combined Health Information Database was discontinued, although most subfiles became available through other means; the search may be refined at the websites listed in the CHID database.

Genetic/Rare Conditions Support Groups (www.kumc.edu/gec/support/). The Genetic and Rare Conditions Site, Medical Genetics, University of Kansas Medical Center provides lay advocacy and support groups, information on genetic conditions/birth defects to professionals, educators, and individuals, as well as to national and international organizations.

COMMENT

In March 2001, the National Institutes of Health issued the following warning: "The number of Web sites offering health-related resources grows every day. Many sites provide valuable information, while others may have information that is unreliable or misleading." Furthermore, because of the rapid increase in Internet-based information, many hours can be wasted searching, selecting, and printing. As an example, we report the data we obtained through an easily performed search on the Google search engine and on the OMIM search engine (December 2008). The following key words were used: lymphedema, congenital lymphedema, lymphangiectasia, intestinal lymphangiectasia, pulmonary lymphangiectasia, chylothorax, chylous ascites, and chylous pericardium. Comparisons between data from the retrieved entries were as follows: Google vs OMIM, respectively, lymphedema (1,140,000 vs 54), congenital lymphedema (126,000 vs 33), lymphangiectasia (39,800 vs 14), intestinal lymphangiectasia (23,600 vs 10), pulmonary lymphangiectasia (12,600 vs 8), chylothorax (312,000 vs 12), chylous ascites (31,200 vs 10), and chylous pericardium (9,960 vs 1). Since only a tiny fraction of useful information dealing with lymphedema can be retrieved by general search engines such as www.google.com or others, this simple example demonstrates that a non-systematic approach to Internet research may not only be time consuming, but it can also be confounding. Although genetic disorders and syndromes are usually thought of as being very rare, their aggregate frequency makes them an inescapable part of medicine. It is vital that affected individuals, their families, and their primary and specialty care

physicians have an accurate and reliable source of information in order to provide the best care possible. Furthermore, with the remarkable surge of information that has become available due to the explosion of the Internet, the networking of researchers and families, the development of support groups, and the availability of research reports and data, it is essential for one reference to contain the bulk of available material organized in an easy to use manner.

Diagnosing congenital lymphatic dysplasia and counseling the parents of babies with possible genetic conditions may represent a difficult task. In this case, the use of a specific database is advisable. In particular, databases that offer images showing patients' features or relevant investigation pictures are very useful. Unfortunately, free website based databases do not provide these valuable services while purchased CD-ROM databases, which are usually very expensive, are certainly more complete. Finally, it can be useful to cite the Consensus Document of the International Society of Lymphology that was published by Lymphology in 2003 (8) or subsequent versions, as the document takes into consideration also the genetic aspects of congenital lymphedema and is updated every four years.

CONCLUSIONS

This article has attempted to provide a guide to establishing genetic tools and a reference library to be used in the diagnostic work-up of congenital lymphatic diseases.

The tools outlined are not meant to replace genetic counseling; their role is merely to facilitate the interaction between lymphologists and geneticists and thereby promote very early identification of lymphatic dysplasias.

These resources may be useful in helping medical professionals, students, and members of the general public who want to conduct medical research using the most advanced tools available while spending the least amount of time doing so. The choice of tools listed is based on our own experience; we avoided taking into consideration books, databases, or websites not personally experienced, used, or consulted by the authors. Qualitative choices and detailed comments about each referenced tool have not been included. Although most of these websites contain current and credible information, lymphologists and other users are encouraged to exercise their own judgment in accessing and evaluating the information.

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