

WORKSHOP EPIDEMIOLOGY
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New approaches in epidemiology in neuromuscular disease

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In Corfu, 23rd May 2002, preceding the MSM- congress a workshop took place focussing on new approaches in epidemiology. This workshop was organised by the WANDA Conte Academy Forum (WCAF), a joint venture of the World Alliance on NMD- associations and the Gaetano Conte Academy.

Purpose of the meeting was to discuss the present situation against the background of the new views on genetic epidemiology in neuromuscular diseases.

Various participants presented data from their own country.

Prof. L. Comi and Y. Poortman chaired the meeting.

This article is a report of the introduction and the discussion that took place.

Genetic Epidemiology; an essential component of gauging the NMD problem and the configuration of therapeutic solutions.

With our increased understanding of the molecular pathophysiology of neuromuscular diseases as well as the advent of novel approaches towards both biological (e.g. gene therapy, anti-sense) and pharmacologic (e.g. combinatorial libraries, high throughput screens) therapies, the definition of the scope of the clinical problem as well as the presymptomatic identification of affected individuals assumes increasing importance.

Epidemiological data on the incidence and prevalence of neuromuscular disorders are the basis for the estimation of the impact for society, policymaking and charting overall healthcare needs (e.g. mechanical ventilatory care, rehabilitation, adaptations, technical aids). Information of this nature is also important scientific groups and for industry embarking on drug exploration and ultimately for pharmaceutical trials. Finally, these data are often required by granting agencies.

There are also many questions which could be answered by assessment of gene frequencies in different countries, by the development of instruments to measure the effects of any preventive intervention or in monitoring effects of pharmaceutical agents and by the longitudinal recording of a selection of relevant patient data.

The present times are exciting for researchers and NMD families; with the cloning of disease genes, previously obscure molecular pathologies are illuminated, drug targets identified, genetically faithful animal models generated.

Two central issues

A commitment to genetic epidemiology would address the issues of disease ascertainment and clinical trial design. The human body is remarkable in its ability to compensate for and therefore mask many disease processes, particularly those that are insidious in their onset. This is of special relevance in the more chronic NMDs such as SMA type II and III. In clinical based epidemiology patients whose symptoms are not yet manifest are not identified unless they are submitted to specific genetic tests for example if they are at-risk relatives of affected patients)

It is expected that new therapies will be most effective if given early, preferably presymptomatically. Genetic epidemiology brings with it the potential to assess the number of individuals bearing a pathogenic mutation before they are symptomatic as well as precise figures about carrier frequencies for such mutations. The second issue concerns difficulties with randomized control trials. Many parents of children with fatal disorders will understandably reject such an approach with its 50% chance of their child receiving a placebo drug. A clear natural history of the untreated disorder is essential to assess the efficiency of a treatment in the absence of a RCT. Rigorous genotype – phenotype correlation will improve such natural history delineation. If a certain longevity or disease course is correlated with a certain genotype, then prospective non randomized non placebo controlled clinical trials become possible.

What is needed.

Genetic epidemiology will involve molecular diagnosis, the formulation and accreditation of accepted diagnostic criteria (ENMC) as well as new activities of associations for neuromuscular diseases and of NMD- specific parental and patient groups to trace families with affected members f.i. by the use of websites. (see table)
Sophisticated new options for performing molecular diagnoses, electronic data collection, storage and management and the easier set up of large scale studies thanks to new communications facilities.

Epidemiological studies of rare disease are hampered by the rarity of the condition, by under or inaccurate and late diagnoses, by lack of money to establish adequate coordinating networks.

In the past many of epidemiological studies were small scale, rather local, diverse in outcome and with limited reliability due to uncertainties in diagnosis, and difficulties in classification and therefore of doubtful scientific quality.

Prof. Emery, former research director of the European Neuromuscular Centre (ENMC) has made a meta analysis of the existing data. The conclusion was that there is a serious paucity of data and a necessity for further coordinated and systematic studies. (A.E. Emery, 1991, population frequencies of inherited neuromuscular diseases, a world survey. Neuromuscular Disorders, 1 : 19 – 29)

It is relevant to consider initiatives for new approaches and joint ventures in epidemiology. Other reasons which support this statement are the general accepted diagnostic criteria thanks to ENMC which allow better comparison and easier communication. New activities of the NMDAs and the NMD- specific parental and patient groups tracing the families with affected members, can largely contribute to this. Moreover there are new approaches such as multi center and multi national studies based on agreed criteria and protocols.

Topics discussed during the workshop

1. Natural history

Longitudinal patient data recording may replace double blind trials which are less and less acceptable for both parents as well as adult patients

2. Genotype-/phenotype correlations

Genotype-/phenotype correlation are necessary as a basis for reliable predictions of the clinical course and the definition of homogenous patients groups for therapeutic trials as well as for the estimation of prevalence figures.

3. Inventory of national medical care facilities/ self support groups

The medical systems are very different in the various countries. In order to plan systematic studies with as complete as possible ascertainment of patients in certain districts, an inventory of medical care systems is desirable.

In this respect activities of national, continental and international NMD- specific patient groups, also expressing their wishes and comments, were thought to be relevant.

4. Development and implementation of powerful therapeutic trial settings

To prepare for availability of promising drugs, trials need to be prepared and the infrastructure has to be implemented on the basis of existing data (e.g. detailed information about the prevalence, the prognosis and course of disease) and a network of centres willing to participate. Self support groups play an important role in the implementation of an effective network.

5. Establishing national and international networks

Regarding the limited number of patients, the variety of pathogenic mutations and the difference according the ethnic background, sufficient amounts of data can only be obtained by international networks.

6. Multi disciplinary coordination and collaboration

Coordination among scientists (e.g. neuropediatricians, geneticists, epidemiologists) is a prerequisite for systematic studies.

7. EU- projects f.i. in the context of VI th Framework Program

The feasibility of submitting an application in the context of the VI th Framework Program of the DG- Research of the European Commission was discussed. This program focuses on “networks of expert centres” and “integrated projects”.

Conclusions of the workshop

Genetic epidemiology was considered of high relevance and large scale collaborative studies realised by national and international cooperating networks were regarded necessary.

ENMC and the ENMC- consortia could take initiatives.

Activities of parent and patient groups and more specifically of WANDA or the WANDA Conte Academy Forum were in this regard considered valuable.