FORUM

European collaboration in research into rare diseases: experience of the European Neuromuscular Centre

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ABSTRACT – An understanding of the possible causes, prevention and treatment of rare, so-called 'orphan disease' requires collaboration in research between different centres with the sharing of information. In the case of neuromuscular disorders (such as muscular dystrophies or hereditary neuropathies) this has been achieved through European collaborative research encouraged and facilitated by the European Neuromuscular Centre (ENMC). The successful example of ENMC provides a model for the investigation of other rare 'orphan' disorders or even rare problems occurring in common disorders.

Most neuromuscular disorders are inherited and serious. They include the muscular dystrophies, spinal muscular atrophy, hereditary neuropathies, disorders associated with myotonia, congenital myasthenias and various myopathies. They account for much morbidity and mortality. However, the majority are rare and for this reason collaboration and sharing of information is essential between different centres and countries. The idea of a unique European Research Centre devoted exclusively to the investigation of rare neuromuscular disorders was initiated in 1987, largely as the result of pressure from the European Alliance of Muscular Dystrophy Associations (EAMDA) with financial support from the Association Francaise contre les Myopathies (AFM)[1]. From these initiatives the European Neuromuscular Centre (ENMC) was established in 1990[2]. It was originally based in Paris but is now located in Baarn, The Netherlands. At first entirely supported financially by AFM, it was established as an independent organisation in 1992 supported by charitable organisations in France, Italy and the Netherlands as well as the Muscular Dystrophy Campaign in the UK. Now major funding is provided by the EU for certain ENMC-established consortia. Additional support for certain workshops has also been provided by the Wellcome Trust and the Rhone-Poulenc-Rorer and Cephalon pharmaceutical companies.

Key Points

Neuromuscular diseases account for much morbidity and mortality, but they are also very rare

Research in such rare diseases ('orphan diseases') is facilitated by collaboration between many centres

The European Neuromuscular Centre (ENMC), supported by the EU, arranges international workshops at which experts from different countries may exchange information and plan collaborative research

ENMC sponsored workshops

From its inception it was decided that the most cost-effective way of encouraging and facilitating collaborative research would be to arrange workshops, each attended by small groups of internationally recognised experts invited to address specific problems, and who agreed to collaborate.

Applications to hold such workshops are submitted to the Secretariat (e-mail: enmc@enmc.org; URL: www.enmc.org). These are then assessed by the Research Committee, consisting of eleven senior medical scientists from various European countries chosen because of their expert knowledge in particular fields (clinical research, pathology, biochemistry and molecular genetics). All applications are subjected to careful peer review. If approved, the applicant becomes chairperson of the workshop and arranges the meeting with the assistance of the secretariat. All workshops are held over a weekend, in order to save on travel and accommodation expenses, at a hotel within easy reach of Schipol Airport. At the conclusion of each workshop a consortium of individuals is established, under the guidance of the chairperson, for on-going collaboration on a specific problem, such as the establishment of diagnostic criteria, gene search or the design of a therapeutic trial. At the conclusion of each workshop a brief summary is posted on the ENMC website for the information of patients, patient organisations and non-specialists (enmc.org and enmc.spc.ox.ac.uk). Subsequently a detailed report is published in the journal *Neuromuscular Disorders* as well as in other medical and scientific journals. To date approaching 100 workshops have been held, covering a wide range of topics. They have been attended by over a thousand medical scientists. Participants, selected because of their expert

knowledge and experience in particular fields, are listed in a 'Who's Who in Europe' of such individuals[3]. It is hoped the information will be useful to researchers as well as clinicians seeking the most up-to-date and detailed information on particular disorders. Though mainly from EU countires, many participants have been invited from outside the EU, most notably from North America, Australia, Japan, Brazil, Israel and Turkey. The number of different countries represented at workshops has increased over time from 5 in 1990 to 20 in 2000, which is a measure of ENMC success since non-Europeans have to participate at their own expense. But most importantly, a number of consortia have gained highly competitive EU funding for on-going collaborative research. The EU has recognised the important role of ENMC in this field by first directly funding workshops, and now as a subcontract partner in several successful projects.

Diagnostic criteria

The establishment of agreed diagnostic criteria for each disorder, or group of related disorders, was given priority from the beginning. This was considered essential since the research results, especially in regard to gene search, would only be meaningful if they related to clearly defined conditions. For example, following early studies which indicated that the gene for spinal muscular atrophy was located at chromosome 5q, some doubt was raised when certain exceptional families were found not to be linked to this locus. However more careful and expert studies of these particular families revealed that they in fact did not have spinal muscular atrophy. Diagnostic criteria for a wide range of neuromuscular disorders have now been established[4] and are continually under review (Table 1).

Table 1. Neuromuscular disorders for which diagnostic criteria have been proposed.

Muscular dystrophies
Congenital
Distal
Duchenne/Becker
Emery-Dreifuss
Facioscapulohumeral
Limb girdle
Myotonic dystrophy
Non-dystrophic myotonias and periodic paralyses
Spinal muscular atrophy
Myopathies
Desminopathies
Myotubular
Nemaline
Mini core and central core
Inclusion body myositis
Mitochondrial
Familial ALS
Hereditary motor and sensory neuropathies (HMSN, CMT)
Chronic inflammatory neuropathies
Post-polio muscle dysfunction
Congenital myasthenic syndromes

Table 2. Muscular dystrophies and myopathies associated with dilated cardiomyopathy (DCM).

Key: *autosomal dominant (AD), autosomal recessive (AR), limb girdle muscular dystrophy (LGMD), Emery-Dreifuss muscular dystrophy (EDMD), Duchenne and Becker muscular dystrophies (DMD and BMD), * – conduction defect may also be present*

Disorder	Gene Locus	Protein Defect
AD DCM	1q	*Lamin A/C
LGMD 1B		
AD EDMD		
AD DCM	2q	*Desmin
LGMD 1D	6q	* –
LGMD 2C – 2F	Various	Sarcoglycans α–δ
XR EDMD	Xq28	*Emerin
Barth syndrome	Xq28	'Taffazin'
XR DCM	Xp21	Dystrophin
DMD		
BMD		

Gene identification and characterisation

Collaborative research facilitated by ENMC has indirectly, and in some instances directly, resulted in the identification of the genes responsible for most of these disorders. This information has led in some cases to the broadening of the diagnostic criteria. This has been particularly so in the case of congenital muscular dystrophy and particularly the limb girdle dystrophies. Several neuromuscular disorders have now been shown to be associated with cardiac disease, most notably a dilated cardiomyopathy (Table 2). This can sometimes be the predominant and most important clinical feature associated with certain gene mutations and resultant protein defects. Several ENMC workshops have addressed this important problem.

The establishment of agreed diagnostic criteria has not only proved invaluable in clinical practice and gene search but also for accurate genetic counselling in affected families. ENMC consortia have therefore addressed such problems as neonatal screening and carrier detection. For several disorders mutation databases have been established, accessible through the Internet.

Management and treatment

As the genes for various disorders have been identified and characterised, so attention is now turning increasingly to problems of management and treatment. This gradual change in emphasis is reflected in the professional backgrounds of participants to workshops, predominated earlier by geneticists, and now more by clinicians concerned with management and therapy (Table 3).

Problems of respiratory insufficiency and ventilatory support have been addressed as well as the possibilities of setting up a unit to co-ordinate therapeutic trials in neuromuscular disorders in Europe. Matters being considered include the organisation of trials, the problems of combining data from different centres (and therefore the need to standardise

Table 3. Professional backgrounds of workshop participant (% for each year).

Professional background	1990	1992	1994	1996	1997	1998	1999	2000
Clinical	18	28	63	26	56	37	45	52
Genetics	67	53	14	39	16	33	19	9
Pathology	5	2	5	4	9	4	7	5
Basic Sciences	6	9	12	14	17	10	18	29
Others	4	8	6	17	2	16	11	5

'Basic sciences' refers to biology, biochemistry, physiology, pharmacology, etc.
'Others' refers to epidemiologists, statisticians, mathematicians, etc.

methodology and outcome measures), the choice of a specific therapy or management to be assessed, the importance of patient and family involvement (including fully informed consent) and how the findings of any study can be made available to other patients and their organisations, physicians and administrators. Discussions on these topics are on-going and it is hoped to set up such a unit in the near future. Currently a European multi-centre double-blind controlled trial of prednisolone in Duchenne muscular dystrophy is being considered under the possible aegis of ENMC. Workshops have also addressed the subject of Cochrane collaboration and the importance of therapeutic trials in multifocal motor neuropathy, periodic paralysis, chronic inflammatory demyelinating polyneuropathy and spinal muscular atrophy. Recently ENMC has also supported workshops on the possibilities of gene therapy and stem-cell therapy. More are planned for the future.

The EU has taken a particular interest in rare or so-called *orphan diseases*, defined as those with less than 5 cases per 10,000 of the population[5,6]. The EU's orphan drug policy will encourage pharmaceutical companies to research therapies for small numbers of individuals which would otherwise be commercially not attractive. The key features of the European orphan-drug policy include support through a Special Committee for Orphan Medical Products (COMP) and assistance from the European Agency for Evaluation of Medical Products (EAEMP).

Conclusions

Over the last ten years ENMC has been successful in initiating, encouraging and facilitating collaborative research into neuromuscular disorders. Many of these disorders are very rare. For example, myositis ossificans (fibrodysplasia ossificans progressiva), an autosomal dominant disorder, is among the rarest of human afflictions with an estimated incidence of less than one per two million births in the UK; there are probably no more than 200 cases world-wide[7]. International collaboration fostered by two ENM C workshops on this topic led to agreed diagnostic criteria and the recognition of several previously unknown affected families for gene studies.

The main value of the ENMC model has been to bring together highly motivated, internationally recognised medical scientists to discuss problems, share ideas and collaborate in basic research and therapy. These small, essentially informal workshops, by concentrating on matters of current medical and scientific interest, and avoiding at all costs the formal presentations where views and data often go unchallenged in most large meetings, have clearly had an effect on the success of such research by fostering international collaboration.

The example of ENMC in regard to neuromuscular disorders could well provide a model for the study of rare 'orphan' disorders in various other branches of medicine or even rare problems occurring in common disorders. Experience indicates that encouraging and facilitating collaborative research in Europe, or more widely, can lead to success which would otherwise not be possible or would take much longer to achieve.

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