INTRODUCTION

Rare diseases are disorders occurring with a low frequency in the general population. They are therefore somewhat neglected from a scientific and social security perspective. They have been recently described as “orphan diseases” because affected patients receive little support from health systems, little research is devoted to discovering their pathogenesis and the pharmaceutical industry is unwilling to finance studies researching specific drugs, which would not have a big enough market to guarantee returns on the necessary investment.

Some of these diseases are hereditary, some are congenital, others have late onset in adulthood or even in ageing; some of them are transmissible, some can be treated, some are rare in certain countries and endemic in others.

A USA law defines a disease as rare if it affects less than 200,000 US citizens (1/1200 persons). Other countries have narrower definitions. In Europe, the Working Group on Rare Diseases instituted by the Commission of the EU defines rare diseases those affecting less...
than 5/10,000 persons. In Japan, the figure is 4/10,000 persons.

Recent WHO data indicates that at least 5,000 diseases and syndromes can be defined as rare. Most of them (about 4,000) are caused by genetic anomalies and prevalently affect the nervous system, with involvement of other systems too.

Introducing a conference on rare diseases held in Florence in March 1999, Prof. Garattini stated that “rare diseases and orphan therapies are one of the many unacceptable inequalities of our health system. A patient with a rare disease is doubly unfortunate: he has a disease like many others but has trouble in finding a doctor expert in his disease. He has the general problem of not having readily available therapies. Finally, his hopes for the future are not good, as pharmaceutical companies are not interested in developing drugs that have a limited market (orphan drugs)” (1).

POLITICAL PROGRAMMES AND RARE DISEASES

In 1989, the US Commission on orphan diseases underlined the state of neglect of this group of diseases and listed several priorities. This was a milestone in the recognition of the right to health care of patients with rare diseases.

The priorities accepted by all developed countries are:
– need for information;
– need for research into pathogenesis;
– need to provide incentives for research and development of drugs;
– need to ensure adequate health care for all affected patients.

All the European countries adopted this line and the Italian Health Plan 1998-2000 identified rare diseases as one of the major health policy problems, recommending the following actions:
– identification of national referral centres and formation of a network of hospital centres for diagnosis and treatment;
– development of a national research programme to improve prevention, diagnosis, health care and therapy;
– development of strategies to improve the quality of life of patients;
– development of a programme of information for patients and their families;
– development of strategies of action for the production of specific drugs in order to improve therapeutic prospects.

RARE DISEASES: HOW MANY ARE THERE?

In 1995, the Physicians’ Guide to Rare Diseases (2) – the Italian translation Guida alle malattie rare (3) was published in 1999 – divided the main rare diseases into various categories and listed the main clinical signs, differential diagnosis, treatment, referral centres in the USA. It was the first example of a book on this subject aimed at general practitioners (GPs). The Italian version (3) has recently been distributed to GPs and general practice paediatricians throughout the country.

Table I shows the distribution of rare diseases across the various medical specialities.

<table>
<thead>
<tr>
<th>Medical Speciality</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic</td>
<td>165</td>
</tr>
<tr>
<td>Connective tissue</td>
<td>40</td>
</tr>
<tr>
<td>Neurological</td>
<td>140</td>
</tr>
<tr>
<td>Endocrine</td>
<td>33</td>
</tr>
<tr>
<td>Immunological</td>
<td>84</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>31</td>
</tr>
<tr>
<td>Metabolic</td>
<td>70</td>
</tr>
<tr>
<td>Ophthalmological</td>
<td>26</td>
</tr>
<tr>
<td>Haematological</td>
<td>70</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>20</td>
</tr>
<tr>
<td>Dermatological</td>
<td>58</td>
</tr>
<tr>
<td>Renal</td>
<td>12</td>
</tr>
</tbody>
</table>
RARE NEUROLOGICAL DISEASES

Due to involvement of the central or peripheral nervous systems or muscle, more than 50% of rare diseases have symptoms requiring specialist neurological care. Neurologists are therefore the specialists most concerned with correct and immediate diagnosis. They have to be familiar with these disorders and to develop a correct approach to patient management (Table II).

The general attitude of families, patients and the health system (family doctors, specialists, hospital doctors) is almost always characterised by a resignation to the situation, by the idea that diagnosis is useless, since no therapy exists. Correct diagnosis is frequently regarded as an academic exercise because the causes of neurodegeneration cannot be cured.

Here we report our experience in a reference centre for rare neurological diseases (Neurometabolic Disease Unit, Research Centre for the Diagnosis, Therapy and Prevention of Neurohandicaps and Rare Neurological Diseases, University of Siena) that, endeavouring to establish diagnoses and therapy, receives patients from various regions of Italy. In the case of neurogenetic diseases, it is sometimes possible to identify healthy carriers and perform prenatal diagnosis in families at risk.

RESEARCH CENTRE FOR THE DIAGNOSIS, THERAPY AND PREVENTION OF NEUROHANDICAPS AND RARE NEUROLOGICAL DISEASES, UNIVERSITY OF SIENA

This centre was founded 3 years ago by a pool of university researchers interested in rare diseases. Its foundation was prompted by the need to offer complete (not only neurological) care to patients with rare diseases. Like other similar centres, we found that even minor health problems can be the source of insurmountable difficulties in the care of these patients as a result of families and family doctors being poorly informed about them. A normal medical problem, easily resolved in patients with common diseases, often triggers a series of management problems that may be insurmountable in patients with rare diseases.

Our staff offers a broad spectrum of expertise, enabling the problem of neurological disabilities to be approached in a coordinated way. The organisational structure of the centre is shown in Figure 1.

Table II - Number of diseases with neurological involvement.

<table>
<thead>
<tr>
<th>Neurological involvement</th>
<th>401/749</th>
</tr>
</thead>
<tbody>
<tr>
<td>No neurological involvement</td>
<td>348/749</td>
</tr>
</tbody>
</table>

(Taken from Ref. 2)

Fig. 1 - Research Centre for the Diagnosis, Therapy and Prevention of Neurohandicaps, Medical School, University of Siena.

The diagnostic approach consists of traditional clinical methods focusing on personal and family medical history, inheritance, course, multisystemic involvement and neurological symptoms. The diagnostic hypothesis is tested by biochemical and neurophysiological examination, traditional imaging (CT, MRI), functional imaging (functional MRI, nuclear magnetic (NM) spectroscopy, PET scan), morphological investigations (skin, nerve, muscle biopsies, etc.), and molecular ge-
We have developed a cell and DNA bank for further pathogenetic investigations.

The diagnosis of rare disease is often a lengthy process for families, involving many hospitalisations in different hospitals. A study conducted in the USA showed that 6 years or more elapse before patients are correctly diagnosed. In our experience, deriving from the patients we have observed in our centre, the mean interval between the first clinical sign and diagnosis is 3-6 years for diseases with infantile onset and 4-10 years for those with later onset.

Table III lists the consequences, nearly always irreparable, of late diagnosis. Improvements in patient management are thus needed to reduce the interval between the first clinical sign and diagnosis. Information on prevention strategies (prenatal diagnosis) needs to be made available to affected families in order to prevent the birth of other affected subjects.

Table III - Consequences of late diagnosis.

- Late onset of therapy
- Genetic counselling no longer possible
- Prenatal diagnosis not possible, leading to birth of other affected subjects

Late diagnosis is nearly always due to lack of information about the diseases, on the part of both family doctors and specialists. Health system structures are needed to obviate the problem of late diagnosis and to facilitate patient and family access.

Table IV lists the main problems we encountered among families and doctors.

Table IV - Rare neurological diseases: problems of doctors and families.

Doctors: 
- Lack of information
- Lack of knowledge of the subject

Patients: 
- Lack of information on the disease
- Lack of support groups
- Lack of information on research and therapy
- Obstacles to use of common health services

Figure 2 shows the pedigrees of two families, one with fucosidosis and the other with metachromatic leukodystrophy. Both families had a first daughter (aged 6 and 3, respectively) with severe spastic tetraparesis and epilepsy, initially misdiagnosed as sequelae of neonatal anoxia, but correctly diagnosed at 6 and 3 years of age, respectively. In the meantime, two sisters were born. They were diagnosed at 8 months and 1 year of age, respectively, before clinical symptoms became evident. Bone marrow transplantation, accepted by one family, produced good clinical and metabolic responses.

Fig. 2 - Two pedigrees with two affected siblings. Early diagnosis may prevent the birth of another affected case.
INFORMATION SERVICE FOR RARE NEUROLOGICAL DISEASES

The Information Service for Rare Neurological Diseases was established in Siena three years ago. Like similar services, it provides information on clinical signs, examinations and tests needed for diagnosis, on referral centres for the different diseases in Italy and abroad, on recent research and addresses of family support associations.

The service has two doctors on its staff and they can be contacted by telephone (0577.585763), fax (0577.40327), e-mail (federico@unisi.it; dotti@unisi.it) and post (U.O. Malattie Neurometaboliche, Servizio Informazioni Malattie Neurologiche Rare, Policlinico Universitario, Viale Bracci 2, 53100 Siena, Italy).

We have received many requests from the different Italian regions and also from foreign countries. The majority of requests are from families, but we have recently had increasing contact with GPs and neurologists.

We are also organising a link with the web page of the Italian Society of Neurology, in order to help Italian neurologists to become familiar with these disorders.

MEDICAL SCHOOL AND LIFELONG TRAINING

One cause of late diagnosis mentioned above was a lack of scientific information reaching family doctors and specialists. The reason for this is that rare diseases tend to be glossed over in courses at medical school. In our opinion, it is essential that family doctors, dentists, speech therapists, physiotherapists, neurophysiologists, nurses and others professionals in heath system acquire (albeit different levels of) information about these disorders. They should at least be aware of the complexity of the problems, the different biological mechanisms that may lead to rare neurological diseases and the sources of information available to them when they encounter cases. At least two hours of lessons must therefore be devoted to this topic in the different medical courses. Obviously, in post-graduate schools of neurology these disorders need to be more dealt with in greater depth.

However, technological innovation and new therapies cannot be forthcoming unless young scientists are trained in basic and clinical research in this sector. In this regard, incentives have been few, due to the lack of specific funds and to the difficulty in recruiting a sufficient number of patients for clinical trials (4). Steps have been taken to overcome these limits with the allocation of specific funds for rare diseases and orphan drugs in the framework of the Biomed projects.

To train personnel specifically for this type of research, a new PhD course (Mechanisms of Neurodegeneration, Neuroprotection and Neuroregeneration in Rare Neurological Diseases) was instituted at Siena University in 1999. The duration of the course is 4 years and links with other European universities (Paris, Oxford, Szeged) have been established. Its aim is to prepare young scientists for research into the mechanisms of neurodegeneration in rare diseases (such as neurometabolic diseases, especially mitochondrial and purine metabolic diseases, and neurogenetic diseases, especially x-linked ones) and into methods of neuroprotection and neuroregeneration, through in vitro and other studies. Rare neurological diseases are considered a good model for investigating the functions of the central and peripheral nervous systems and muscle.

PROBLEMS RELATED TO THERAPY: THE EXAMPLE OF CEREBROTENDINOUS XANTHOMATOSIS

Certain rare neurological diseases, especially those linked to neurometabolic dysfunc-
tion, may benefit from different therapeutic strategies: for example diet, aimed at reducing toxic metabolites reaching the nervous system and other organs (phenylketonuria, aminoacidopathies, organic acidurias, mitochondrial diseases, and so forth); drugs, designed to antagonise toxic substances; replacement therapy, aimed at correcting enzyme deficiencies by providing vitamin cofactors or directly replacing the missing metabolites (carnitine in carnitine deficit, vitamin E in vitamin E deficiency, etc). However, the treatment of rare diseases presents many problems, particularly in relation to the development of new drugs (4).

Cerebrotendinous xanthomatosis (CX) is a rare neurometabolic disease that we have been studying for many years (5). Most Italian cases of this disease are treated in our centre. The clinical characteristics of CTX include progressive mental deterioration leading to dementia, juvenile cataract, epilepsy, myopathy, peripheral neuropathy, heart anomalies, osteoporosis and tendon xanthoma. These manifestations are secondary to a metabolic disorder of bile acid with low plasma concentrations of chenodeoxycholic acid and high concentrations of cholestanol, a cholesterol derivative that replaces the latter in the plasma membrane, rendering it unstable and dysfunctional. The metabolic condition is due to a deficiency of liver 27-hydroxylase activity. The gene coding for the enzyme has been identified and many mutations have recently been described, some by our group. It has been demonstrated that if normal bile acid concentrations are restored by administration of chenodeoxycholic acid (750 mg/day), serum and CSF concentrations of cholestanol decrease and clinical symptoms improve (6). If therapy is started at an early stage, this treatment prevents severe neurological symptoms. Homozygotes can be diagnosed before symptoms appear by identifying mutations of the gene coding for 27-hydroxylase.

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Table V - Chenodeoxycholic acid therapy in cerebrotendinous xanthomatosis.

<table>
<thead>
<tr>
<th>Problems</th>
<th></th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs previously available in pharmacies: Chenochoi, Chenofalk, Chenoxy, Fluibil</td>
<td></td>
<td>- Centralised distribution allows clinical and biochemical monitoring</td>
</tr>
<tr>
<td>Problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Unavailable since 1995</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Only ursodeoxycholic acid available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ursodeoxycholic acid does not reduce plasma cholestanol levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Galenical preparation by Siena hospital pharmacy</td>
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Chenodeoxycholic acid was used in the therapy of bile stones and was available over the counter in pharmacies. It became unavailable in Italy in 1995, with the introduction of other drugs, such as ursodeoxycholic acid and simvastatin, for the treatment of bile stones. Ursodeoxycholic acid does not reduce plasma levels of cholestanol and therefore cannot be used to treat CTX. Simvastatin is less effective than chenodeoxycholic acid in reducing plasma levels of cholestanol and has many side effects. As a result, our patients (a total of about 40), were suddenly deprived of a vital substance that prevented disease progression.

Fortunately we found a drug company that produces the substance for other purposes, and in collaboration with the our hospital pharmacy, we galenically produced appropriate doses of the drug for our patients. The drug is now distributed to all patients periodically, enabling us to carry out clinical and biochemical monitoring, and making our referral centre therapeutic as well as diagnostic (7).

The data gathered over the years have provided useful information on absorption, metabolism and side effects of the drug in a significant
group of patients, and on some of the metabolic pathways of cholesterol and cholestanol.

CONCLUDING REMARKS

Our experience has taught us that in spite of many initiatives at national and international level to facilitate diagnosis, research and therapy of rare neurological diseases, much still needs to be done in support of these patients, who are doubly unfortunate: first because they are ill and secondly because of the difficulty of obtaining medical care.

One aim of a modern society should be to ensure that basic and clinical research is conducted into this group of diseases, which can also serve as useful models for understanding normal functions of systems of neurons, glial cells, muscle cells and so forth. Another aim should be to ensure that research is conducted into diagnosis, therapy and prevention and that doctors and patients are provided with adequate information. These aims can be realised through increased funding, coordination of basic and applied research, availability of epidemiological data and disease records, and above all through collaboration between the doctors, biologists and technicians working on these problems and patients and their families awaiting therapies to improve their quality of life.

ACKNOWLEDGMENTS

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REFERENCES