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Lesson No. 6

Reducando Digital Education

Rare diseases in Italy.

What am I? The main questions, in the presence and online, of parents.

A disease is **rare** when its prevalence, i.e. the number of cases present at a given time in a given population, does not exceed a certain threshold. In Europe, a disease with a prevalence of 1 in 2000 is considered rare.

Rare diseases are a complicated issue for public health, for the legislator, for the citizens, for the sick and for their families, and for the professionals involved in directing health interventions to the real needs of patients. Prevention of disability and premature mortality, early detection of disease (early diagnosis), availability of treatment, improvement of the quality of life and social and working of citizens with rare diseases and their families are still the most important challenges to be faced.

In Italy since the early 2000s legislation has been introduced to protect patients with rare diseases. In the course of the development of the legislation, it was necessary to identify the conditions under which appropriate safeguards could be ensured. A **list** that includes about **900 diseases** has therefore been established. Although this number seems to deviate from the numbers that have been reading for years on rare diseases, the Italian list probably includes almost all the rare and disabling conditions that are observed. In any case, the legislation provides for regular updates to include new diseases that meet the defined rarity criteria.

In Italy, a lot of attention is paid to **rare diseases**: **national and regional registers** have been set up to collect the data of patients to whom protection measures are extended. These registers are very important because they can provide reliable data, and not just estimates, on the prevalence of different diseases.

Epidemiology

According to the most recent estimates, in **the world**, among individuals suffering from a rare disease would be more than **300 million** and in 70-75 % of cases, they would be subject to pediatric age (in other words, they are children). In **Italy**, estimates of the number of people with a rare disease speak of **1-2 million subjects affected**, while those relating to the percentage of pediatric patients report that the latter account for about 70 % of all carriers of a rare disease. In our country, according to Orphanet Italy, a portal dedicated to rare diseases, people suffering from these diseases would be about 2 million, but these are estimates.
Patients with **rare diseases**, and their families, also face the difficulties caused **by the chronicity and disability** that characterize many of these conditions. In European health systems, including the Italian one, expensive medicines and hospital care are provided free of charge, but many **costs (we think of individual care, transport, many aids) can weigh heavily on people and families** who, due to the disease, cannot work.
In Europe and worldwide, measures have been taken to promote the **development of orphan medicines**, which, without specific incentives, the pharmaceutical industry would generally have no interest in developing. The reason is that these would be targeted at a limited number of patients, with an economic return, therefore, less than

the investment needed to develop them. These drugs are unfortunately very expensive and for this reason in many countries, they are not even available: this leads to a disparity in access to care, which is not quite acceptable today.
Scientific research is the only possible hope for rare diseases.
The main obstacle to their prevention, diagnosis and treatment is the lack of knowledge, which for many rare diseases is insufficient or zero. It is only by encouraging basic and clinical research that we can hope to obtain treatments and treatments that are increasingly effective for **rare diseases**.

What is the origin of a rare genetic disease? or metabolic?
What unites these totally different diseases is a rarity; so talking about "one cause of rare diseases" is not possible. But we can say that there is another aspect that allows us to unite the vast majority of rare diseases: their **genetic origin**. It is generally estimated that over 70 % of rare diseases are determined by a **genetic mutation**.

Many other conditions are acquired and the genetic mechanism leading to the appearance of the disease (in pathogenetic jargon) is known: for example, many autoimmune diseases are rare.

For others, finally, the cause is still unknown to date and we often do not even know data on incidence and prevalence.

The cases:

The causes of rare diseases include:

Genetic mutations: A genetic mutation is a stable change in the characteristic DNA sequence that constitutes a certain gene. Genetic mutations are at the origin of most rare diseases. Examples of **genetic diseases**, rare diseases due to genetic mutation are **congenital conditions**, i.e. present since birth;

Chromosomal disorders: A chromosomal alteration is a stable anomaly caused by a certain chromosome; located within the nucleus of the cell, chromosomes are the particular structures into which the entire DNA is divided. Since chromosomes contain several genes, chromosomal alterations are responsible for changes in the sequence of multiple genes. Just like rare diseases due to a genetic mutation, rare diseases resulting from chromosomal alteration are congenital conditions belonging to the large category of genetic pathologies.

- **Infectious agents**. Infectious agents that cause rare diseases include bacteria, viruses, fungi and parasites. Rare diseases due to the action of an infectious agent are examples of **rare infections**. • **Allergic reactions**. Rare diseases resulting from an allergic reaction are examples of **rare allergies**.
- **Degenerative processes**. In degenerative processes, a certain organ or tissue loses normal anatomy/histology. Rare diseases due to the degeneration of a certain organ or tissue are examples of **rare degenerative diseases**.
- **Proliferative processes of the neoplastic type**. Neoplastic proliferative processes are events where excessive and uncontrolled growth of cells belonging to a certain tissue or organ occurs. Rare diseases due to the uncontrolled proliferation of a certain cell line are examples of **rare cancers**.

Symptoms

In general, rare diseases are conditions characterized by a wide **variety of symptoms and signs,** which often causes the bearers of the same condition to experience sometimes very different disorders.
Some rare diseases are pathologies that appear at birth and in the first years of life; other rare diseases, on the other hand, appear only in adulthood. The mode of occurrence of a rare disease depends, basically, on the causes.

What does rare genetic disease mean?
The (national) list of rare diseases consists of 80 % **genetic diseases** and, for the remaining 20 %, conditions such as **infections**, **allergies**, **diseases of a degenerative nature** (e.g.: neurodegenerative diseases) **proliferative**

diseases, better known as **tumors**;
Rare diseases, therefore, are mostly pathologies resulting from the mutation of one or more genes; To date, the number of rare diseases known ranges **between 7,000 and 8,000**; however, it should be pointed out that this figure is constantly growing, as doctors have increasingly effective diagnostic techniques in recognising conditions that are still unknown;
As a rule, rare diseases are **debilitating** conditions with a chronic/permanent character or with **fatal consequences**; As the availability of adequate treatments is in the interest of few patients, the scientific and medical community devotes little time and little economic resources to seeking new treatments against rare diseases known so far.
This is the main reason why people suffering from a rare disease, hardly, can rely on therapy, which has purposes other than simple "management" of symptoms;

Where rare diseases are not the subject of scientific research and where there is no adequate treatment for them, experts shall define these conditions as **orphan diseases**. A disease is called an orphan when it is rare, when it does not arouse particular scientific interests and, finally, when those suffering from it cannot count on adequate treatment. About 50 % of known rare diseases do not benefit from a foundation aimed at finding suitable treatments.

What does rare metabolic disease mean? Freely taken from:
https://www.osservatoriomalattierare.it/malattie-rare/malattie-metaboliche- Observatory Rare Diseases **Metabolic diseases** are a heterogeneous group of rare diseases caused by a specific deficiency of one of the metabolic pathways. These are diseases caused by an alteration of those biochemical processes that allow the cell to use and break down substances such as carbohydrates, proteins and lipids into simpler compounds to obtain energy. Metabolic diseases are more than 1400, and some of them still difficult to diagnose. Today**, however, for more than 40 metabolic diseases there is the possibility of extended neonatal screening**, which allows for recognising diseases that can result in very serious disability when not diagnosed at birth and immediately treated. For information on **the exemption codes for** metabolic diseases, you can consult the appropriate

Guide.—https://www.salute.gov.it/portale/home.html

The main questions, in the presence and online, of parents; e-mail: centroservizimalattierare@gmail.com (a p63 International E.E.C Syndrome service),
RARE- C.S.M.R.
Contact us:

- **Tel: + 39 3333063353**
- **www.csmr-centroservizimalattierare.eu**
- **centroservizimalattierare@gmail.com**
- **Facebook page**
- ***My baby has a rare disease. What should I do?***
- ***I suspect my baby has a rare disease. What should I do?***
- ***My baby has so many unknown symptoms. Could it be a rare disease?***

These are the main questions that a parent asks when they come across the family problem of a child with a rare illness, in Italy and for our associative experience and that comes to our Rare Disease Services Center.
Let us highlight immediately the different situations caught by the questions on the state of knowledge of the rare disease: • **"my child has a rare disease"; this means that parents are familiar with** the type of rare illness of their child and fully or partly understand the related problems of health and quality of school and social life; the most important obstacle that patients still face today is the **lack of specific and definitive care**. Rare diseases, in fact, are largely caused by genetic defects that cannot yet be repaired. For now it is only possible to remedy, when possible, the alterations caused by such defects. In many cases, you can: for example, some **metabolic** diseases such as *Gaucher's disease* or *Fabry's disease*, both caused by a genetic

defect that causes an enzyme to malfunction. The consequence is an accumulation of molecules in some cell organelles called *lysosomes* that alters the functioning of the cell (and thus organs). Both diseases are now treated with the administration of the enzyme produced in the laboratory, which replaces the defective one. This does not eradicate the disease but significantly reduces signs and symptoms, and manages to attenuate or stop the progression of organ damage.

There are many other examples of how research in recent years has found solutions to other rare diseases, but there are also many others for which no effective treatment can be seen.

- ***"I suspect that my child has a rare disease",*** means that the suspicion arose in parents by observing their child or teacher, or from the analysis of the doctor of families/pediatricians, or informed friends. For many years rare diseases have had an important feature in common: the difficulty in being recognised. The limited knowledge of the symptoms and specific signs of many rare diseases by family doctors, as well as many specialists, has led to the difficulty of reaching a diagnosis soon. Although it is always possible, today the risk of the so-called "diagnostic delay", for which a patient remains for a long time without a diagnosis, has significantly decreased, thanks to:
- greater attention of doctors to unusual forms of the disease;
- increasingly digital attention of young parents in the search for answers (not always targeted and often improper on the web)
- the development of investigative knowledge and techniques, especially in genetics;
- the dissemination and usability, especially almost universal digital, of scientific information tools;
- the tireless work of raising awareness by rare disease patient associations is an indispensable reference for parents and teachers, often also for doctors and research centres.

"***My baby has so many unknown symptoms, could it be a rare disease? "*** Freely taken from: https://www.issalute.it/index.php/la-salute-dalla-a-alla-z-menu/m/malattie-rare HigherInstitute of Health.

There are many rare diseases united by the complexity of clinical manifestations but very different from each other in terms of the cause and evolution of the disease (hetiopathogenesis), the present disorders (symptomatology) and the organs involved.

About 80 % of them have genetic origins (i.e. it involves one or more genes or chromosomes) and may be hereditary (the disease is transmitted by parents) or derived from a so-called *de novo* mutation, in other words not inherited from the parents but the result of a "new" event that occurred for the first time in that specific individual. Of the remaining 20 %, one part is determined by infections (bacterial or viral) and autoimmunity or due to so-called *teratogenic* factors (chemicals, radiation, etc. that could cause foetal damage); the other comes from the interaction between genetic and environmental causes.

The age of onset of disorders (symptoms) can vary greatly. Certain diseases may occur at birth or in childhood, such as many metabolic pathologies; others, such as amyotrophic lateral sclerosis, occur only in adulthood.
The people who suffer from it, despite being very different diseases, share the same difficulties linked, precisely, to rarity. They shall include:

- *difficulty in obtaining the diagnosis (diagnostic delay),* between the appearance of the first disorders (symptoms) and the detection of the disease (diagnosis), may sometimes pass long intervals of time, during which the disease is not recognised or a wrong diagnosis is made. These cases create considerable inconvenience for the patient and his family and often lead to inadequate therapies
- *high costs of treatment (therapies) and diagnostic tests, and the high cost of dealing with the rare disease, from detection (diagnosis) to therapies, combined with the lack of social benefits and the possibility of reimbursement of all healthcare costs*, causes a general impoverishment of the family and dramatically increases the differences in accessibility to treatment for patients with rare diseases
- *deficiency or absence of appropriate (therapeutic) care,* rare diseases are often chronic and disabling, may involve multiple organs or apparatus (multi-systemic) and sometimes cause early mortality. For these reasons, they require the involvement of several specialists together, in the health and non-health field. However, only a small percentage of them can count on resolutive therapies and adequate medical

attention

- *differences in the availability of care (therapies)***and care***,* innovative therapies (which propose new therapeutic approaches) are not always available in all EU countries in the same way. This depends on delays in the pricing of medicines and/or decisions on their free offer (refundability) by the national health service; the absence of guidelines or recommendations relating to treatments and therapies
- *often insufficient scientific knowledge,* and lack of in-depth scientific knowledge often leads to great difficulties in developing appropriate therapeutic strategies
- ***little available information*****, the information available to the citizen, often incomplete and from unreliable and non-institutional sources, makes it difficult to navigate precisely between doctors, clinical reference centres and support services.**
- ***Social hardship,*** **living with a rare disease has consequences in every field of life, in school, in work, in leisure, in relationships with friends or in emotional life. It can lead to social isolation until the actual exclusion of the sick person from the community in which he lives**
- *difficulties in the transition from pediatric age to adulthood,* progress made by science (in diagnostic techniques or new treatments/pharmaceuticals) has led to an improvement in the evolution over time of many rare diseases and, consequently, an increasing number of patients reaching adulthood. This new, positive situation necessarily requires the availability of trained professionals who can also provide adults with health and social care just as specialized as that provided to children so far.

Rare diseases studied- freely taken from TELETHON ITALY:

https://www.telethon.it/cosa do/research/diseases-study/

Consult the factsheets on diseases on which we have funded at least one research project since 1990. In the first years of activity we also supported projects on diseases of a multifactorial nature, in the following years we invested in **diseases of proven genetic origin**. The material is prepared and updated with the support of our researchers and patient associations, **but does not replace medical advice**

Curiosity: definition of Rare diseases in other parts of the World

- In Japan, all those conditions that affect 1 in 2,500 individuals are called rare diseases.
- In the United States, all those diseases that affect 1 in 1,500 people are reported as rare diseases.

Did you know that...

Statistics say that every 17 individuals there is one that, at a certain stage of its existence, will develop a disease included in the list of rare diseases. Compared to the number of inhabitants in Europe, one clinical case per 17 people corresponds to 7 % of the total population.

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