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Why rare diseases?

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Summary. Patients with rare diseases are awaiting an answer to their needs. Traditionally, however, research on rare diseases has been limited by the idea that it was too difficult to do and too little rewarding in terms of return of profit. This attitude has actually changed during the last decade, because it was realized that research on rare diseases may help finding solutions valid also for common conditions. Indeed, while we all invoke translational research as the way to adapt results of laboratory studies into therapeutic interventions for patients, rare diseases often need the opposite path: we observe rare patients in the clinical practice, then we find out that they have a genetic defect, and finally we reproduce the defect in an animal model to extend the observation further beyond the clinic. In the process we also learn a lot about the physiology and the pathology and have insight into the mechanisms of common diseases. In other words, studying a rare condition may enlighten the path to other discoveries and to break the boundaries between disciplines and specialities to provide solutions for the sake of the patients.

Key words: rare diseases, clinical research, translational medicine.

Riassunto *(Perché studiare le malattie rare?)*. I pazienti affetti da malattie rare sono in attesa di una risposta ai loro bisogni. Tuttavia la ricerca sulle malattie rare è stata tradizionalmente limitata dall'idea che fosse troppo difficile da condurre e troppo poco remunerativa in termini di profitto. Questo atteggiamento è di fatto cambiato durante l'ultimo decennio, poiché si è realizzato che la ricerca sulle malattie rare può essere di aiuto nel trovare soluzioni valide anche per malattie comuni. Infatti, mentre la ricerca traslazionale viene classicamente intesa come il trasferimento dei risultati degli studi di laboratorio a interventi terapeutici, le malattie rare hanno spesso bisogno del percorso inverso: osserviamo i pazienti affetti da malattie rare nella pratica clinica, ne identifichiamo l'alterazione genica e la riproduciamo in un modello animale per estendere l'osservazione oltre la clinica. Durante il processo impariamo molto sulla fisiologia e la patologia e abbiamo una visione di insieme dei meccanismi delle malattie rare. In altre parole, lo studio di una situazione rara può portare alla luce un percorso che porta ad altre scoperte e superare i confini tra le diverse discipline per fornire soluzioni per la salute dei pazienti.

Parole chiave: malattie rare, ricerca clinica, medicina traslazionale.

INTRODUCTION

Patients with rare diseases are awaiting an answer to their needs of improved diagnosis and treatments. We believe that more research, either basic and clinical, is needed to adequately answer to those requests [1].

However there are several limitations to this end, one of the most important being the limited investments in the field. It has been felt for years by public institutions, funding bodies, private industry, that research on rare diseases is not worthwhile: too difficult to do and too little rewarding in term of return of profit.

This attitude has actually changed during the last decade or so, because it was realized that research on rare diseases may help finding solutions valid also for common conditions.

AN INTRIGUING PAIR OF TWINS

In our clinic we have had recently the chance to see a young lady of 21 years of age. She had renal insufficiency and proteinuria. One of her kidneys was occupied by several cysts full of fluid. The absence of cysts in the liver, lack of family history for kidney diseases suggested that she was not affected by autosomal dominant polycystic kidney disease.

This girl had an identical twin. Their mother said that this second girl was doing fine. She had only a problem with her sight when she was a child, but not with her kidneys. One twin had kidney disease, the other eye problems *(Table 1)*.

We asked to visit also the sister of our patient. Indeed we found that she also had some problems with her kidneys, although very mild.

What puzzled us was that two identical twins, who

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Table 1 | *Clinical presentation in two homozygous twins*

Propositus	22 weeks of gestational age	Multiple cysts of the left kidney
	Birth	Renal Insufficiency
	21 years	ESRD (GFR 20 ml/min/kg)
Twin	2 years	Visual acuity loss Normal renal function
	21 years	Renal function tests?

Table 2 | *Renal coloboma syndrome: clinical features*

65 cases
Kidney hypodysplasia with renal insufficiency
Optic nerve coloboma
Mutations of PAX2 gene in about 50% of the patients

shared the identical DNA, had such different clinical manifestations.

Their disease is actually the Renal Coloboma Syndrome [2]. There are 65 cases in the world. This is a genetic disorder caused by a mutation in the PAX2 gene. Our patients had a new mutation, never described before *(Table 2)*.

What is intriguing in the story of these two sisters is obviously the presence of two very different phenotypes while the genotype is absolutely identical. This may be explained by studying the epigenetic mechanisms of the disease. A mouse model of the disease could be of help. Indeed a mouse with a PAX 2 mutation, determining an animal counterpart of the renal coloboma syndrome is now available for studies. This is an interesting example of what is called translational research. Only, the other way around.

THE CASE OF TRANSLATIONAL RESEARCH

We all invoke translational research as the way to adapt results of laboratory research into clinical studies and then in effective therapeutic interventions in patients. We are not denying the importance of such a journey, but rare diseases often needs the opposite path: we observe rare patients in the clinical practice, then we find out that they have a genetic defect, and finally we reproduce the defect in an animal model to extend the observation further beyond the clinic.

In the process we also learn a lot about the physiology and the pathology and have insight into the mechanisms of common diseases.

Again, another example from the field of kidney diseases. The renal glomerulus is a wonderfully built anatomical structure, that helps us to get rid of the wastes from the body, and regulate the fluids and electrolytes.

Several years ago, a Finnish boy, who was swollen since his birth, was loosing great amounts of proteins in the urine, and his renal function was impaired. His disease was called congenital Finnish Nephrotic Syndrome [3].

Researchers found that this boy had a mutation in the gene that encodes for a protein, nephrin, which is essential for the normal architecture of the glomerular barrier.

This first discovery of one component of glomerular wall has open the path to a very fruitful research area, which has then lead us to a better understanding of the normal anatomy of the kidney and may help in the future to find new treatments for a variety of glomerular diseases.

A RESEARCH CENTER FOR RARE DISEASES

Our interest for rare diseases dates back in the mid eighties, when the Clinical Research Center for Rare Diseases "Aldo e Cele Daccò" was first conceived (it became fully operational few years later) *(Figure 1)*. Since then we have been interested in studying a rare condition called hemolytic-uremic syndrome (HUS). This disease is characterized by hemolytic anemia and microangiopathy,

Fig. 1 | *Aerial photograph of the Clinical Research Center for Rare Diseases Aldo e Cele Daccò, Ranica (BG), Italy.*

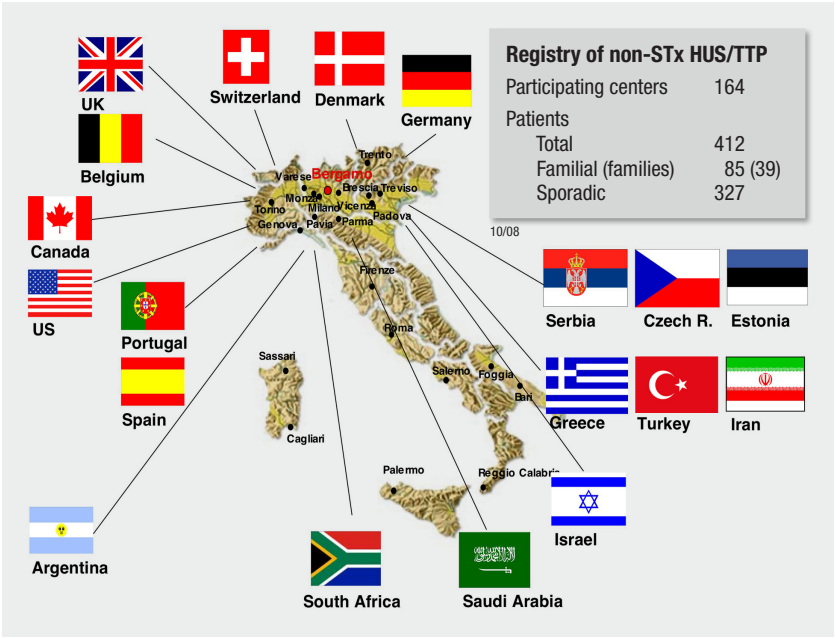

Fig. 2 | *Hemolytic-Uremic Syndrome International Registry: participating centers.*

and may lead to chronic renal insufficiency. Most cases are described in small children after an episode of acute gastroenteritis when the causative agent is a particular kind of *E. coli*. Much rarer are the forms of HUS that are not related to an infection but are due to genetic abnormalities. These forms are collectively called atypical HUS.

Several years ago we have established an International Registry *(Figure 2)* which allowed us to collect patient data from all over the world. This registry is not only a repository of clinical data, which are very important to make correlations between clinical events and outcome, but also a collection of biological samples, extremely precious biological samples, we would say [4]. This is an example on how we can realize international collaborations between centers of expertise, having the patient data and samples travelling, and not the patients themselves. This also reminds us that seldom patients need to move, and even less so outside our country: for almost any single rare disease we have all the expertise we need in Italy.

HUS is a disease that has several variants, each characterized by a specific mutation in one of the genes that encode for the complement components. Several groups in Europe are collaborating in this field, for example we have closed links with researchers in Newcastle (UK), and Barcellona (Spain). Together we carry on sequencing of the putative genes responsible for the disease, and then we make clinical correlations [5, 6].

We have found that some mutations are associated with a favourable outcome. In other patients, the disease proceeds until the renal function is completely lost and there is the need of renal replacement therapy. In some of these patients renal transplantation, which remains the best option for renal replacement therapy, is contraindicated because of the high risk of relapse. The basic genetic defect, in fact, is not corrected after the renal transplantation and the consequence is the loss of the graft.

For these reasons it is important to study each patient with atypical HUS in order to find out if his/her variant is the one that predispose to the failure of the transplantation. If this is not the case, transplantation is an option, but not for all the other variants.

Recently, it has been proposed that a drug developed for a rare disease, nocturnal paroxymal hemoglobinuria, may be useful in patients with atypical HUS who would be bound to graft failure. The complement C5 inhibitor eculizumab is the object of several clinical trials in atypical HUS. These studies may result in a new indication for this otherwise very costly drug, expanding its use and may be leading to a reduction of its cost, which is now in the order of 300 000 $ per patient per year.

Time will tell us whether this new treatment is effective in HUS. However, this story has already taught us something: research in rare diseases is an unexpected source of new ideas. Studying a rare condition may enlighten the path to other discoveries and to break the boundaries between disciplines and specialities and lead to solutions for the sake of the patients [7].

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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