

Patient Associations: a driving force for Rare Diseases research. Resilience: a driving force for Patient Associations

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Abstract

Until a few decades ago, Rare Diseases were relatively unknown. Their low prevalence made them invisible to public opinion, and were of little concern to researchers and pharmaceutical industries. Rare disease sufferers and their loved ones had become victims of the disease as their implications were overlooked. Consequently, some of these individuals formed associations and embarked on ways to change this situation of neglect they had found themselves, in finally having their rights recognized. These associations have over time gained important roles in planning public health and biomedical research, especially after the introduction of the Human Genome Project. Their active participation and awareness activities have been crucial in establishing reliable Rare Diseases Registries and related Biobanks, essential tools in fully utilizing the data and the new omics technologies derived from the Human Genome Project in the field of Rare Diseases.

The founders and members of these associations have a high degree and considerable ability to face the difficulties of life, while also maintaining a positive attitude and a confident vision, best defined as resilience. Not everyone, and not always, is endowed with a resilience capability. However resilience can be improved or reinforced through appropriate training and intervention programs. This review points out specific programs centered mainly on mindfulness.

Introduction

Rare Diseases (RDs) are so defined for their low prevalence; they broadly affect at the most 1 in 2000 people, with some of these even affecting less than ten people in the entire world. Yet RDs are not so rare: the World Health Organization (WHO) estimates that there are approximately 6000–8000 rare diseases, and more still to be discovered, which affect more than 80 million people (corresponding to about 6–8% of the world

population) (1, 2). Most of these are serious chronic diseases, which hinder the quality of life, cause severe disabilities and are life-threatening.

RDs represent a huge health problem for the number of people involved, for their related social burdens, and the unmet needs to be fulfilled that are still immense (3, 4).

Eighty percent of RDs have a genetic origin, or have a genetic component. Others derive from multi-factorial determinants, such as exposure to infectious agents or toxins

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and, occasionally, from adverse responses to therapeutic interventions (1, 5).

The RDs low prevalence represents the major stumbling block for an effective and successful management of these diseases and biomedical research. The development of safe and effective drugs and medical tools for the prevention, diagnosis and treatment depends on reliable data, and ultimately the low number of people affected with any rare disease, hampers the recruitment of adequate research cohorts suitable in obtaining robust scientific results (5, 6).

The low prevalence and the low representativeness of samples available have disheartened even the most ardent researchers in the field. Moreover, the difficulties in attracting public and private funding for research and development has resulted in a lackluster interest in progressing further to better characterize RDs.

However, in the last few decades, Rare Diseases Patient Associations (RDPAs) have managed to overcome this state of neglect (6, 7).

Moreover, the achievements of the Human Genome Project and the derived *omics* technologies have already been exploited in discovering and characterizing disease hampered RDs genes (8, 9). Most of these findings have taken advantage of the data of Rare Diseases Registries (RDRs) and of specimens from Biobanks dispersed all over the world. The creation of reliable RDRs and Biobanks are dependent on motivated patients, resolute to share their personal data to realize a common, scientific and therapeutic project (10, 11).

These issues make the RDPAs indispensable for RDs research and management.

Self-help Groups, Rare Diseases Patient Associations

In the last few years, since the second half of the last century, numerous RDPAs

have been formed, with the main purpose of establishing support networks of support solidarity to achieve better care, and improvement of the quality of life of patients with many different rare pathologies (7, 12).

In some respects, these associations may in part be assimilated into self-help groups (SHGs) that have developed in the last century, particularly in the field of dependence, psychiatric disorders, some serious organic pathologies, overcoming mourning, and other situations (13, 14). The first self-help group was that of Alcoholics Anonymous (AA), an association established in Akron, Ohio, U.S.A. in June 1935, and then spread to many other countries over the course of more than 80 years. The purpose of this association has always been for the treatment of alcoholics, mainly through group therapy and mutual help. The effectiveness of AA interventions has been recognized by doctors, psychologists and by specialists in the field, operating in health centres, hospitals and universities (15).

RDPAs have represented and still represent a model in which the groups endeavor to overcome marginalization of illness and suffering. In addition, these groups permit to experience membership, mirroring, exchange, and sharing, countering the emphasis on individualism that often characterizes the culture of our time.

RDPAs, like all SHGs, have arisen due to existing public service deficiencies, or in opposition to these services, and hence are often an alternative (7). Therefore, very often the relationship with scientific medical experts was, especially in the beginning, somewhat conflicting, a position well expressed by the editorial board of the British Medical Journal (BMJ), which in reply to the Society for Mucopolysaccharide Diseases: 'the editorial board at the BMJ does not enter into correspondence with lay people' (16).

In addition to physicians, healthcare providers and researchers, also Pharmaceutical companies are important *counterparts* of the RDPAs. These companies are known for their obvious economic interests, they had and some still have a reluctance to consider research and sale of pharmaceuticals that are for the care of only a few patients (7).

For the mentioned reasons, the reputation of the so called *professionals* have not always been highly appreciated by RDPAs; therefore, patient groups, healthcare providers and pharmaceutical research have not always moved in the same direction and for the same intended objectives.

Up until a few years ago, the interaction trends between *professionals* and self-help groups and patient associations could be attributed to three predominant models:

- co-operation: professional workers (doctors, healthcare, researchers, and others) working together with patient and family groups;
- support: group work involving patients and family members with the exclusion of professionals, except for third party support situations;
- separation: group work conducted and initiated by patients and family members; with their insistence of excluding professional operators.

Fortunately, in recent years the tensions between *professionals*, and patients and their relatives, have diminished, and the co-operation model has prevailed, especially in the field of rare diseases. This co-operation model is not based on the submission of one of the parties, but based on a process in which one recognizes that both parties play an important role in improving the physical, psychic, and social conditions of patients (7, 10).

This aspect is even more important in the post-genomic era, mainly considering the post-genomics medicine approach, principally based on the analysis and comparison of a myriad of molecular-*omics* data (17, 18).

In this respect, the conscious involvement of RDPAs and their active collaboration with physicians and scientists can make the difference by sharing their information and expertise to overcome the paucity of data regarding RDs (9, 17, 19).

Patient Associations, Rare Diseases Registries and Post-genomics medicine

The Human Genome Project has opened new frontiers for gene discoveries and characterizations, and the Internet has favored the spreading of all kinds of information about RDs, raising more awareness about the needs and what can be done today in fulfilling them (19, 20). RDs research has benefited from the breakthroughs of the post genomic era and its *omics* technologies, which have provided innovative protocols to study RDs families with only a few affected individuals, possibly speeding up gene discoveries and characterizations (8, 18). Moreover, these new research potentialities have stimulated the interest of scientists towards RDs investigation, and the latest computational tools along with the Web communication have revealed powerful means to collect, use, share and exploit research and personal data (21). Networks of scientifically relevant resources are being created for many RDs, covering multiple domains such as clinical, personal and genomics records (22). Most of these networks are founded on committed RDPAs and on the appropriate use of Rare Disease Registries and Biobanks (10, 23, 24).

The post-genomics medicine approach requires analyzing the molecular, phenotypic and lifestyle data of thousands of subjects to give a correct perspective of individual molecular pathways, and patient registries represent the right reservoir where to source these data (1-4, 10). Patient registries may provide information on family history, onset of the diseases, and clinical tests outcomes.

RDPAs can galvanize the attention of patients explaining to them the purposes of RDRs development and encouraging them to share personal and illness information. The informed patients acquire awareness of their role and, therefore, may provide their personal data, fundamental for planning appropriate research projects.

Recently, some registries have been linked to Biobanks, and therefore they may also contain molecular-*omics* data (25). These data are crucial for selecting the appropriate trial strategies and for the computation of the final results of the clinical studies (26).

These patient registries potentialities are even more relevant in the RDs field where the scarcity of information is the stumbling block for basic treatment and clinical research. These are being explored and exploited by numerous scientific and medical designs involving RDs research and management (27).

In Europe, for instance, the International Rare Diseases Research Consortium is devoted in linking genomic data with registries, Biobanks, and clinical bioinformatics tools to produce a central research resource for RDs (28, 29). In the USA, the NIH/NCATS Global Rare Diseases Patient Registry Data Repository program is pursuing the goals to gather and link together patient information from many different registries and biorepositories for RDs (30). These ambitious projects aim to build up a Web integrated platforms to collect genomic and clinical patient data from many RDs registries and store them in a unique, extensive registry for RDs linked to a centralized database for rare bio-specimens. These data may be used to complete research projects and may help to discover new disease genes, pathways, and therapeutic targets. These projects require new computational tools to integrate, in a common structure, data from different registries and from different Biobank catalogues, always with the protection of privacy in mind when

linking medical and personal data. Though ambitious, these projects represent the appropriate platform of the required data and information to gain reliable results in RDs basic and translational research (31, 32).

Moreover, RDPAs are collaborating with researchers, industries, healthcare services and public agencies to increase awareness of RDs, and to be a presence and to participate all over the world (33, 34).

Each group possesses a great amount of information, painstakingly collected over the years regarding the best qualified health centers and the most advanced therapeutic and diagnostic approaches for the supported diseases. Additionally, patient organization members are often leading experts into the new frontiers of biomedical research, and thus have an even more important participative role in the RDs patient organizations in the future (33, 34). A good example being, the latest approaches regarding Castelman diseases (35, 36). Castleman disease (CD) is a group of heterogeneous inflammatory disorders characterized by abnormal proliferation of lymphocytes (35).

To improve research and management of CD, Frits van Rhee and David Fajgenbaum have founded the Castelman Disease Collaborative Network (CDCN, gathering together researchers, physicians and patients. The co-founder Fajgenbaum is a patient himself. The CDCN aims to spread and share information among the community members. Its main objective is to coalesce researchers and patients, inviting them to discuss and highlight together, the most relevant research targets to achieve in overcoming the paucity of funds and samples available for a reliable omics research in the CD field. For the CDCN philosophy, funds, data, and samples are patrimony of researchers as well as that of the patient community (36).

RDPAs actions are highlighting the participation and cooperation relevance among patients, families and all health

stakeholders, with their commitment considered as a driving force in the field of RDs post-genomic research.

Resilience, strength of patient associations

At this juncture, after stressing important technical and scientific aspects, it is necessary to point out that the commitments of RDPAs affect people and, in particular, people who are in a highly emotionally disposition (37).

All the diseases, especially the most serious, create pain, discomfort and suffering for those affected and their loved ones; specially in the case of rare diseases, which could occur from childhood, a particularly painful and distressing for the whole family. Yet, sometimes, these people have succeeded in managing their anguish and implementing useful and effective operational strategies to claim their rights, not only to improve their conditions (7).

These positive and proactive behaviors of RDPAs members can be described, inter alia, by considering and deepening the concepts of vulnerability and resilience (38-41).

Both for patients and family members, the state of vulnerability is significantly high for rare diseases: in addition to organic disorders linked to specific pathologies, RDs often cause emotional fragility, problematic and dysfunctional behaviors, possible antisocial attitudes, and other conditions. The fragility conditions of patients affected by these circumstances often create very painful moods and emotions in the family, such as disappointment, disbelief, anger, depression, sense of helplessness, guilt, and isolation (38-41).

Hence, in these obvious physical and psychological discomforts of these individuals, claiming their rights necessitates the ability to face and confront the difficulties as they arise, preserving their potential and

positive aspects of life - that is a remarkable resilience. The American Psychological Association (2014) defines resilience as ‘the process of adapting well in the face of adversity, trauma, tragedy, threats or even significant sources of stress (para. 4)’ (40).

Resilience can thus be defined as, ‘maintaining high levels of vivacity, positive moods, and well-being in the face of adversity and/or hardship’ (40).

Resilient people highlight an affective style, represented by the ability to regulate negative emotions by reducing the duration of negative affects when they occur. It is not that resilient individuals do not experience negative affects, but for them these negative affects do not persist, and additionally they experience positive affective states and moods. Resilient subjects can thus approach unpleasant experiences without capitulating, and instead developing more adaptive and effective behaviors.

The tendency to distance painful feelings is replaced by a *spaciousness* of the mind to move towards challenges, overcoming difficulties, and reacting positively to negative affective states.

Resilience can also be described as, ‘*the art of getting back on the overturned boat*’ (39).

Abbey Mayer knew well, ‘*the art of getting back on the overturned boat*’; this attributed to her enormous resilience enabling her to fight for her son’s rights (7).

The Meyers’ son was suffering from Tourette’s syndrome, and was undergoing medical treatment of a clinical trial drug already in test for another more common disease. The drug worked well for Tourette’s syndrome, but not for its original intended purpose. Consequently, the manufacturer of the drug had stopped its production; as the suffers of Tourette’s syndrome were considered not a good market to invest in. Meyers did not accept this explanation, and stood up for her son’s rights. She interacted with the Food and Drug Administration, sent

letters to the major journals and involved many other families having the same urgent needs (7).

In the end, Meyers' struggles pushed the pharmaceutical to reconsider its decision and restart the drug production.

Moreover, Meyers' achievements encouraged other parents and patients to engage in their own battles founding the National Organization of Rare Disorders (NORD).

Resilience can be learned and strengthened

What Abbey Meyers experienced is the emblematic example of how resilience plays an important role in the birth and growth of patient association groups. Meyers had the ability to stimulate public opinion by using all available means of communication, without ever surrendering in facing difficulties. Certainly, one cannot expect every member of any rare disease association to have a comparable resilience, as that of Abbey Meyers; however, a will to join a group denotes a desire to have faith in confronting grave difficulties.

It should be noted that resilience can be enhanced by learning *coping* and adaptive behaviors (41-44). In the case of the RDs family members, it is important to work on the possibility of reorganizing roles, resources, and skills within the family. Being a member of a group can be decisive: to be able to reflect in similar situations, encouraging a continuous exchange of experiences from which new and effective ways to confront and overcome difficulties occurring from time to time (7, 12). Additionally, patient associations today include experienced medical doctors and psychologists who can help strengthen resilience of their members with strategic approaches based on deepening scientific knowledge and awareness of their emotional resources.

With regards to awareness of emotions, one of the ways that is most effective in developing resilience and strengthening coping skills, is undoubtedly based on *mindfulness* (41-47).

The term *mindfulness* is the central aspect of meditation practices predominantly of a Buddhist matrix, and involves a refinement of the ability to pay attention through a constant and profound awareness. Through systematic exercise of self-observation, one can become intimate with their own experience, intentionally suspending their judgmental tendencies, and reducing the use of their automatic repetitive behaviors, often dysfunctional. Therapeutic use of *mindfulness* has been thoroughly investigated, among others, by Dr. Jon Kabat-Zinn, a US hospital physician. From his studies and clinical practice, the Mindfulness-Based Stress Reduction (MBSR) program was created. It focused on regularly held group sessions, and concentrated primarily on reducing and managing stress in its various forms through *mindfulness*, having the objective of increasing the awareness of ongoing events. In the first instance, *mindfulness* tends to change, not the contents of the mind, but our relationship with those contents. It is through an immediate observation, intuitive, and non-judgmental that automatic repetitive behaviors derived from painful affective-cognitive contents are progressively less and tend to fade. Mindfulness-based programs tend to act on reducing automatic repetition of thought (43, 45).

Another model, also consisting of group sessions based on predefined protocols, is Mindfulness-Based Cognitive Therapy (MBCT), which represents an integration of *mindfulness* with some cognitive psychotherapy techniques. The main theorists of this program are Z.V. Segal (psychiatrist), J.M.G. Williams (psychologist), and J.D. Teasdale (psychologist and researcher). This program focuses more on the resolution of psychic problems, such as depression, in

its various forms, and its relative relapse tendency (46, 47). These programs are centered on *mindfulness*, but not only that, they can also be a form of *attention and care* for oneself, through which one can reach a type of *intrapersonal tuning* that fosters resilience. Therefore, group sessions (similar to group psychotherapies with a high psycho-educational component) are recommended in which knowledge and skills can be acquired through firsthand experience. Intellectual knowledge can be useful, but is inadequate. To maintain and reinforce the health effects of the programs, there are useful periodic *recalls* which may also consist of *intensive* periods of one or more days, predominantly of group sessions. The efficacy of the MBCT program has been demonstrated through a randomized controlled clinical trial, with the aim of lowering relapses in depression (46, 47).

The two programs mentioned (but possibly also others) can be used in RDs patients and relative associations. It is certain that they could benefit patient family members in reducing stress and acquiring problem solving skills, and with the main goal of enhancing resilience (44). They may also be effective for adult patients, after psychological sessions, focusing on deeper adaptive skills and individual motivations for each person.

Conclusion

The RDPAs have been founded mainly to overcome the isolation of patients and their loved ones and to share the thorny problems related to RDs management. However, they have been changing their role and aims over the last decade, striving for more information, appropriate diagnosis, effective treatments, and financial support for medical expenses (7, 12, 37). Additionally, several patient groups also collaborate with health professionals and researchers, and their influence as decision makers is increasing,

as is their role in building up RDRs. Moreover, some regulatory achievements on RDs and orphan drugs management have been facilitated by strong and effective engagement of patient organizations.

All this was possible, as members of patient associations and their families have always been firmly resolved in claiming the rights of those who support, or have rare diseases. They have had the ability to go ahead in a sure and courageous way, despite having to face difficult and painful situations. This ability is resilience, understood not only as an attitude to reducing the negative affects once they occur, but also to maintain high levels of positivity and health in the face of adversity (39-45). Without the association members' willpower, none of the achievements made to date would have been possible: they fought against the ignorance of pharmaceutical sector; they met with institutional bodies, and collaborated with doctors and researchers. Resilience is a capacity that can also be acquired and/or enhanced through training and programs that are centered on *mindfulness* (47).

More than two thousand years ago, Hippocrates stated, 'The art has three factors, the disease, the patient, the physician. The physician is the servant of the art. The patient must co-operate with the physician in combating the disease.', underlining the importance of the physician-patient alliance against disease (48, 49).

In some respect, the RDPAs new premises and roles revive the Hippocratic advice; however, the extent of this partnership has not strictly followed the recommendations of the Greek Scientist.

In a recent paper, 'Moving from Patient Advocacy to Partnership: A Long and Bumpy Road', Durhane Wong-Rieger underlined that RDPAs had to struggle for their right to be participants in decision making regarding RDs management and research (50).

On the contrary, Hippocrates always encouraged his pupils to seek for, and to

motivate patients' cooperation. Fortunately, researchers and physicians today have started to accept the acknowledge derived from the experience of those who personally live and face the diseases. However, physicians and researchers should never overlook the pressure of living and dealing with RDs, and they should always take care of the psychological attitudes of patients and their loved ones in facing and coping with the illness, as Hippocrates advised, 'the brain is the most powerful organ (messenger to consciousness) of the human body' (49).

Conflict of interest statement

The authors declare no conflict of interest.

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Riassunto

Associazioni di Pazienti: forza vitale per la ricerca sulle Malattie Rare. Resilienza: forza vitale per le Associazioni di Pazienti.

Fino a qualche decennio fa, le Malattie Rare erano quasi del tutto sconosciute. La loro scarsa prevalenza le rendeva quasi invisibili all'opinione pubblica e di nessun interesse per ricercatori ed industrie farmaceutiche. I malati rari ed il loro cari, invece, subivano dimenticati le conseguenze della malattia. Alcuni di loro si sono riuniti in associazioni ed hanno intrapreso percorsi per modificare la situazione di abbandono in cui si trovavano e vedere finalmente riconosciuti i propri diritti. Queste associazioni, nel tempo, hanno acquisito ruoli molti importanti nella pianificazione di interventi di salute pubblica e nella ricerca biomedica, specialmente dopo il compimento del Progetto Genoma Umano. Un loro coinvolgimento attivo e consapevole può essere determinante nel realizzare Registri di Malattie Rare affidabili e relative banche biologiche, strumenti essenziali per il pieno utilizzo delle nuove tecnologie "omics" nel campo delle Malattie Rare.

I fondatori ed i soci di queste associazioni presentano, ad elevata percentuale, una notevole capacità di fronteggiare le difficoltà della vita, mantenendo anche affetti positivi e una visione "fiduciosa". Questa impor-

tante capacità viene definita resilienza. Non tutti e non sempre siamo dotati della capacità di resilienza che però può essere migliorata e/o rinforzata attraverso opportuni training e programmi di intervento. Vengono segnalati nello specifico programmi centrati prevalentemente sulla mindfulness.

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