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Mal de Meleda: A great imitator

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Abstract Mal de Meleda is an hereditary palmoplantar keratoderma named for the Mljet Island in Croatia. The lives of those affected by this disease represent a complex situation that encompasses members of a vulnerable group. They require enlightenment and should be approached with awareness, taking into account their overall psychophysical status and the environment of each patient. Those afflicted with Mal de Meleda not only have to deal with a difficult life due to their affliction, but they also must cope with the hardships of socialization while trying to realize a normal life within their island community. This is compounded by the frequent interviews and examinations of researchers interested in the various aspects of their illness. The subject of this contribution is not about the nature of this disease, rather about the traces it has left on the (sub)consciousness of the population. It is also concerned with exploring ways of how to access patients and understanding the depth of their vulnerability. We present some thoughts tied to the interpersonal experiences of researchers and patients afflicted with Mal de Meleda.

Introduction

Mal de Meleda (also known as keratosis palmoplantaris transgrediens et progrediens or the Mljet disease) is a hereditary palmoplantar keratoderma named after the Mljet Island in Croatia. We shall focus on the perception of Mal de Meleda, because, in essence, it imitates the mechanisms of behavior and perception about leprosy in the population. These mechanisms are manifested by the stigmatization of the patients and their self-isolation, not only when diagnosing Mal de Meleda (eg, the diagnosis given by Oscar Hovorka) but also in new research (eg, the resistance to comprehension in research, etc).

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Leprosy isolation of diseased and stigma

Stigmatization is frequently related to the disease. A number of examples from the Dubrovnik region of Croatia confirm this, and one of the most blatant examples is the behavior toward leprosy patients. Although not a single reliable record of this disease dating to medieval times or earlier has been preserved for this region, the medieval Statute of Dubrovnik dating to 1272 offers us insight into its presence and how it branded the afflicted. Here is an extract translated into English:

> *We demand that leatherworkers, who live in the place where lepers have used to live, should build themselves solid houses so they would not pose a threat to the commune. Lepers cannot live there anymore and they have to move further away from the city.*[1]

This is a very early example of how the afflicted residents were separated from a healthy community. It also provides an example of early strategies for the prevention of contagious diseases. In this respect, stigmatization has been based on the concept of sin and sinfulness (*spoiled identity*), and so excommunication justified the threat posed to the entire community, which further compounded the emotions of guilt and shame in patients. For clear evidence, we refer to the fact that part of Dubrovnik (at present day Peline), where the lepers were required to live, was also called Guidecca in the vernacular language.[2] This symbol of isolation and punishment for sin was the only proper place for those who were disqualified from social acceptance and, in 1377, laid grounds for the original Dubrovnik invention—the quarantine after the plague epidemic of 1348 to 1349.[3]

The stigma associated with leprosy had a profound impact on the collective memory, such as that it was common for other diseases that occurred in later periods and that could not be rationally explained, to be associated with this illness. A good example is Mal de Meleda, which was called leprosy by the island's population. It was also qualified as such by some researchers at the end of the 19th century, as, for example, by Oskar Hovorka (1866-1930).[4] Historically, it was a Dubrovnik physician, Luko Stulli (1772-1828), who first provided an excellent description of this illness in 1826 (Figure 1). He clearly differentiated it from infectious diseases, as well as emphasizing its hereditary component and epidemiologic spread on the island.[5] In spite of this, the populace continued to believe in its connection to sinfulness. Folklore continuously contained notions of how the disease could be suppressed only by prohibiting marriages—that is, by destroying the seed that is shadowed by damnation.[6,7]

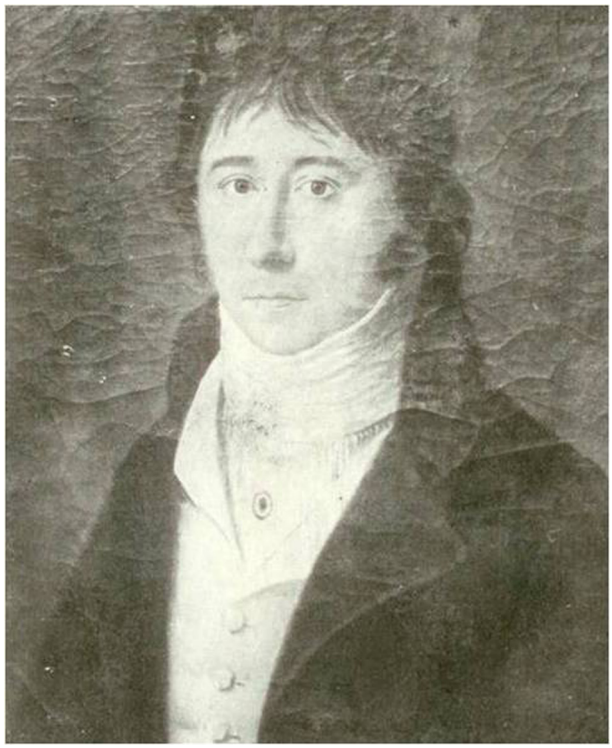

Fig. 1 Luca Stulli (1772-1828), Croatian physician who first described Mal de Meleda. A portrait by Carmelo Reggio, Italy. (Reproduced from Kogoj.[20])

Leprosy colors myths and legends about Mal de Meleda

There are a number of legends tied to Mal de Meleda, and one of them relates to the Mljet pirates who fell ill after having attacked a Turkish ship with leprosy patients near the island of Mljet. They killed the crew and divided the spoils, and so God's wrath fell upon them, and ever since they wore the irreversible mark of shame on their hands and feet.[8–10] The next legend states that, upon returning from the Crusades, the crusaders left all the soldiers who were suspected of leprosy on the islands of Mljet and Lastovo. The afflicted crusaders quickly perished on the island of Lastovo, whereas those on Mljet survived. They were able to bring over marriage partners from the neighboring mainland and so create offspring to whom they transmitted the disease that was no longer infectious as it was initially.[11–13]

The historiography of Mljet and Lastovo as quarantine islands was also the starting point for contemporary research. One of them, published in 2011, started with the analysis of gene polymorphisms associated with the risks of contracting leprosy. It confirmed and scientifically demonstrated the theory of how Mljet really did serve as a quarantine for people with leprosy, or rather of how the so-called "protective alleles" prevail among the population who presently lives on the island, an allele that protects against contracting leprosy. It was the first such study carried out on a European population (up until then, research was carried out only on Vietnamese, Brazilian, and Indian populations) and the first study to be based on the historic existence of a leprosarium in an isolated population. The study confirmed how the infectious disease killed all those who did not have a protective mutation that in some manner prevented them from falling ill or made them, at least, less inclined to illness.[14]

Leprosy, a powerful stigmatizing disease, thus brought something positive by creating the space and setting the stage for new insights into the disease and genetic research; however, the mark left on the collective consciousness of the population was not easy to erase. On the contrary, it sensitized the population with similar feelings of guilt and shame even when dealing with Mal de Meleda, and even more so as these two diseases were occasionally equated with each other.[4,6,11] Considering the presence of Mal de Meleda on the island of Mljet over the centuries, it is cited in literature as a disease having long continuity and a layered history. Contemporary research, which includes determining its comprehensive clinical features and genetic analysis, is less than a few decades old. Up to the present, a number of contemporary studies on

Mal de Meleda have been published,[15–17] and more recently, it has been the subject of a bilingual synthesis[18]; however, the subject of this presentation is not about the nature of this disease, rather about the traces it has left on the subconsciousness of the population. It is also concerned with exploring ways of how to access patients and to understand the depth of their vulnerability; therefore, in this contribution, we present some thoughts tied to the interpersonal experiences of researchers and examinees or patients afflicted with Mal de Meleda, and we will point out the mainstays of ethical treatment for patients.

Vulnerability of patients and resistance to cooperation

Those afflicted with Mal de Meleda have to cope not only with a difficult life due to illness, but also with the hardships of socialization and trying to realize a normal life within their island community, while being continuously and thoroughly examined at the same time by researchers interested in the various aspects of their illness. Research projects that include the afflicted add to their vulnerability and could cause resistance to any kind of cooperation. The lives of those affected by Mal de Meleda are a typical example of a complex situation that encompasses members of a vulnerable group who need to be enlightened and approached with awareness, taking into account the overall psychophysical status and the environment of each patient. An important task in fostering ethical conduct is to determine the nature of a moral reason, which reveals the direction of desirable activities for the stigmatized and for those practicing stigmatization. According to Richard Hare, the moral reasons, which specify the criteria for moral values in concrete situations, must have an objective foundation and must rely on a deductive ethical insight that is derived from the virtues and principles of action.[19]

Mljet has been the starting point of many studies whose aim was to focus on the nature, expression, and possible treatment of Mal de Meleda; however, researchers were constantly confronted with the vulnerability of the afflicted, with explicit or hidden stigma, and with inhabitants who either wanted to speak out or to avoid it, such that there are few insights into this issue. For this reason, we will look at some details and personal observations made by the dermatologist Ana Bakija-Konsuo, who spent time conducting research on the island of Mljet several times at the end of the last century and early this century.

Preparations for individual field research were lengthy and required numerous preparatory visits to the island and its inhabitants, visiting those afflicted and their families to explain the reason for coming to the island and why they were being asked (again) to provide blood or tissue samples and to participate in research that some had already undergone previously. More often than not, it was thought that the research and writing about Mal de Meleda always emphasized the "other" side of the island, renowned for its beauty. Each new return to their illness once again provoked new frustrations, feelings of helplessness in the afflicted, as well as potential belief that they were being turned into experimental subjects.

Stigma and research: Experience with patients during research

Mal de Meleda is branded not only on the skin of the afflicted; it also carries the name of the island, thereby becoming a mark of identification and association with the population, which bears the full weight of the stigma and the psychologic burden. All this is accompanied with a particular feeling of rejection, which can change temporarily only when researchers show an interest in the afflicted, often provoking anger, suspicion, mistrust, and sometimes even resistance.

Getting close to patients and their families to carry out the research was extremely demanding, even in situations when they had already met the researchers and gained a certain amount of confidence. The afflicted emphasized how they frequently felt they were treated as "*experimental rabbits that were interesting only when someone from the country and/or world remembered to write a scientific paper.*" Many of the local government authorities provided significant assistance during the initial research work—in particular, by the former mayor of the Mljet Municipality, as well as by a family medicine doctor, a local priest, and some other acquaintances living on the island. Some members of afflicted families agreed to communicate only after having being persuaded by those mentioned above. In spite of everything, one adolescent, born in 1990, remained out of reach, as neither the adolescent nor the family would even consider participating in the research.

Similar experiences were recorded also by earlier researchers. Franjo Kogoj (1894-1983), a dermatovenerologist, conducted research in Mljet on a number of occasions during the second half of the last century. He expressed his gratitude to the doctors in those times, but also to the leaders of the local community, who assisted him so that families would not hide their afflicted members as was customary, as they considered them to be marked.[20]

During 2004, Ana Bakija-Konsuo conducted research on the quality of life for patients living on the island of Mljet and in Dubrovnik. The results of this research have not as yet been published, even though the preliminary results were reported during the 2nd Croatian Congress of Psychodermatology held in Zagreb in 2008. This research concluded that the quality of life for patients with this disease was significantly reduced. They were subjected to feeling shame and uneasiness on a daily basis, and felt that those around them considered them to be dirty and contagious, frequently emphasizing "*how many would not even want to shake hands with them*." They cited shame as being the biggest issue of their disease, placing it in front of all the obligatory and facultative clinical manifestations of the disease.

Alongside this, patients with Mal de Meleda also pointed out the hardships in establishing emotional and sexual ties, particularly in the choice of a marriage partner. Considering that they were familiar with its hereditary nature, they proudly emphasized which families had daughters-in-law or sons-in-law who came from other islands or the mainland.

Considering that we are dealing with an agrarian population, the afflicted have great difficulties in carrying out work in the fields, primarily because Mal de Meleda results in painful wounds that would hamper work, and due to frequent superinfections. Most of the diseased died at a greater age (above 70 years), and so it can be concluded that age does not affect life expectancy, but it does lead to a worsening of clinical manifestations (Figure 2).[21] The functionality of joints in the hands and feet lessened due to pronounced contractures, which would for some lead to the amputation of some fingers of the hand (Figure 3) and the need for someone's assistance in daily life.[17]

Social networking: Help to cope easier with the disease

To help a patient come to terms more easily with the disease itself, it is important to constantly point out and to encourage the need for communication between patients, as well with all those who deal with this problem.

Even though the number of those afflicted with Mal de Meleda throughout the world is small (less than 200),

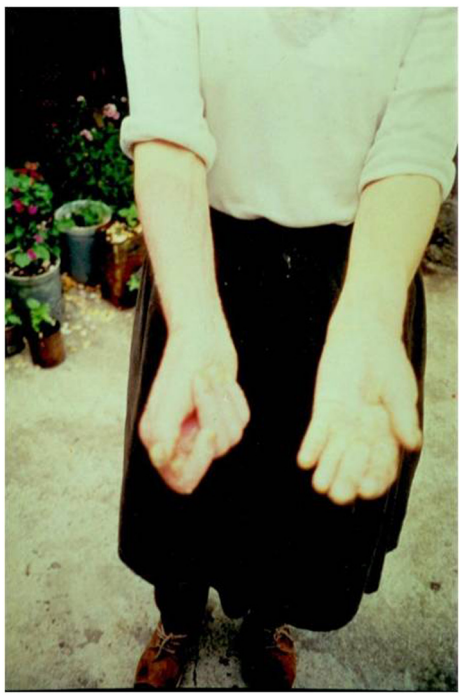

Fig. 2 A typical clinical picture of a patient with Mal de Meleda from the island of Mljet.

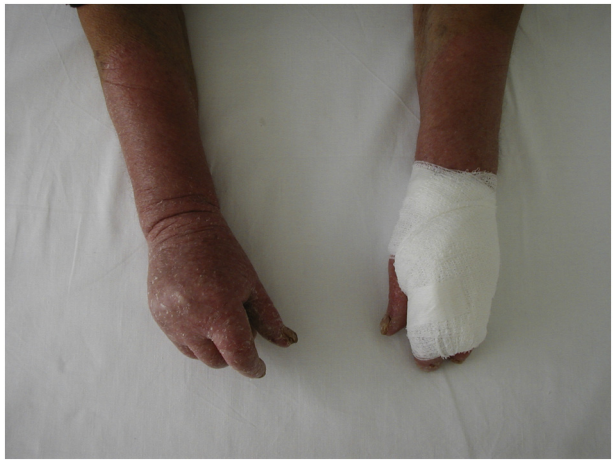

Fig. 3 The hands after amputation of the fourth and fifth fingers in our patient from the island of Mljet. (Photograph courtesy of Dr. Naredlli-Kovacic).

encouraging the creation of associations (like numerous other associations) would contribute to their coming together, communicating with each other, exchanging experiences, and thus making it easier to cope with the disease. Contemporary developments in technology also contribute to easier communication between researchers, doctors, and patients, for example, by using virtual associations or closed social groups (Facebook, Twitter, etc) where the administrator could be a dermatovenerologist. This is confirmed by the example of two patients from neighboring states who contacted a dermatovenerologist via social media networks a few months ago, seeking information on new breakthroughs in the treatment (Figure 4). Family members of the afflicted, as well as physicians dealing with this issue, could additionally contribute to an exchange of information.

Unfortunately, the therapeutic options available to us in everyday practical work do not sufficiently help in improving the clinical outlook and functionality of the affected extremities (Figures 5 and 6). Although it is unlikely that gene therapy will be available in the near future due to the small interest of pharmaceutical companies (based on the small number of patients), getting closer to the patients, understanding their problems, helping with the treatment, and explaining new scientific achievements and therapeutic options could significantly change the relationship toward the disease and the afflicted, as well as toward research and researchers.

Ethics and morality in terms of the vulnerability of patients affected by Mal de Meleda

Mal de Meleda is manifested by a medical connotation that encompasses a clinical picture and an overall approach to its treatment, as well as by psychologic and social connotations. Its psychologic connotation refers to the subjective impression of a patient who feels bad due to chronic mental and physical

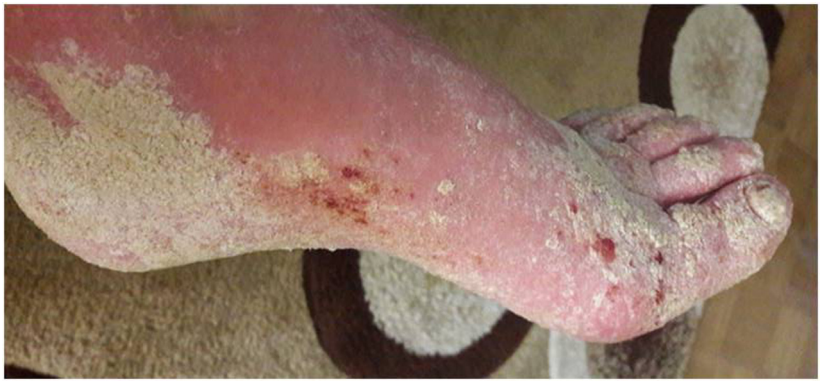

Fig. 4 The foot of a patient with Mal de Meleda from the neighboring country, before starting therapy.

pain or discomfort. The patient is aware of the unattractiveness of his or her appearance and must permanently endure the feeling of being marked by illness. In its social connotation, Mal de Meleda refers to the fact that patients provoke reactions from the community where they live due to their appearance or behavior. This can vary from either acceptance to isolation, or even rejection, ruthlessness, and abuse.

The psychologic and social connotations of Mal de Meleda are valuable expressions, which may be either correct or incorrect, depending on whether the nature of the judgment is based on feelings or reasoned opinion. A medical connotation is valuably neutral as it rests on objectively verifiable research and other, narrowly scientific criteria of truth. Mal de Meleda, in its medical connotation, represents the most important segment, as each step in the development of medical science offers new answers to the questions that preoccupy patients the most. The psychologic and social connotations of the disease largely depend on what is going on in the field of medical science; however, the psychologic and social side of this issue would be further complicated if all new scientific and medical knowledge on Mal de Meleda remained reserved only for academic circles.

All new knowledge, skills, and learnings need to be included and applied in an ethical way, just as Kant suggests: the principle of autonomy consists in maxims (subjective aspirations) being included in the universal law because the will of each rational being is necessarily linked to universality—universality is its condition. By understanding reason in this manner, it is possible to discover correct moral principles; therefore, instead of partiality the moral reason must lead the will as such a stance is analytically true.[22] Kant wanted to say to treat the patient in accordance with the best knowledge, exclude any kind of bias, or disregard toward the autonomy of the patient, and promote sensitivity toward psychologic and social issues in society (such as the acute issues with Mal de Meleda), which is an ethical duty. Knowing and practicing ethical communication can be understood only by those who understand how one can contribute to the reduction of human suffering through personal action, particularly toward vulnerable groups. If we take such moral reasoning seriously, then we will easily approve the stance advocated by Bambrough, who claims that everyone has to account for the interests of others and to prescribe a similar process for everyone. As it is contrary to reason to do harm to oneself, it is also contrary to reason to do harm to others. Consequently, anyone who practices irreversible behavior acts incorrectly or irratio-

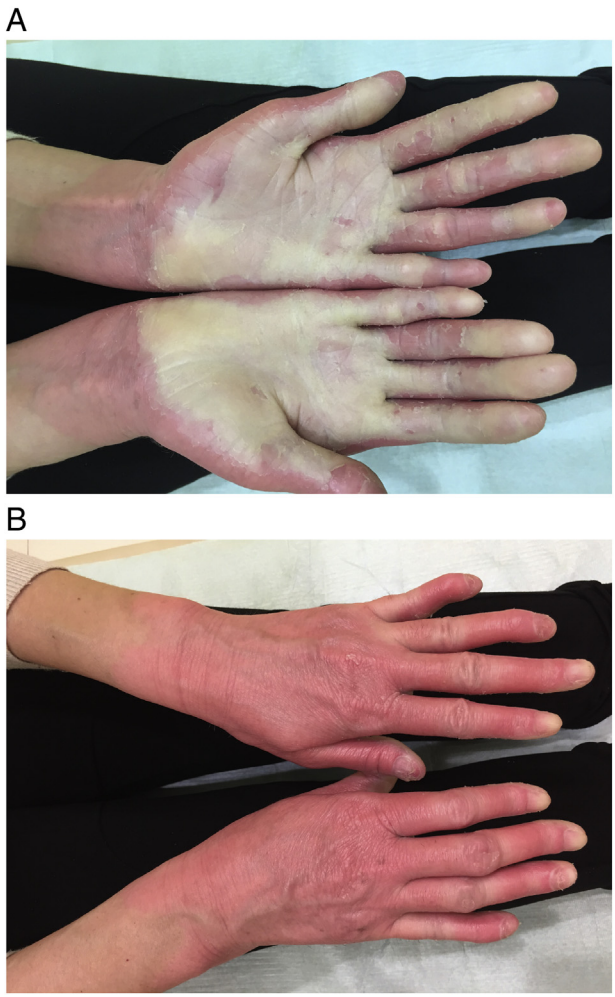

Fig. 5 (A, B) The clinical appearance of the hands after 8 months of therapy with acitretin. Note the reduction of dermatogenic contracture.

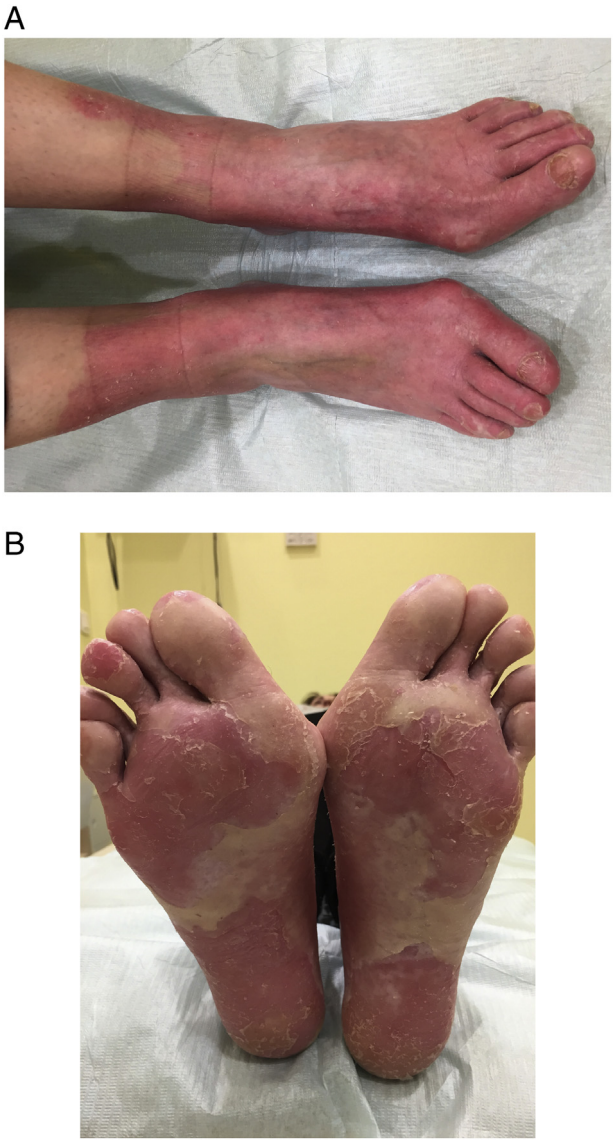

Fig. 6 (A, B) The clinical appearance of the legs and feet after 8 months of therapy with acitretin. Note the reduction of hyperkeratosis.

nally.[23] According to Richard Hare's claim, impartiality is not enough—everyone must be willing to give others the importance they give to their own personal interests—and the human status of a moral subject cannot be avoided. Although not everyone maintains moral principles, moral principles apply to everyone.[19]

In such studies in which collaboration with patients is vital, it is necessary to elaborate an approach of access and communication. Inappropriate attitudes or procedures toward patients are unacceptable and not due to sanctions, but rather concern the disregard of the principles of fairness and equality as well as the dismissal of the need for moral growth. If we ask why we even need moral growth, then the answer is: if we want ethics to influence our moral decisions, then it cannot remain neutral, as it must promote the realization of true values. In this process, the education of interviewed patients is of great importance in terms of offering insights into new methods of their treatment. The studies carried out on Mal de Meleda were greatly assisted by a fact that was continuously stressed by the inhabitants of this island, which is that even though the disease is eponymously named after the island, it never belonged exclusively to Mljet, not even today. Magdalena Nardelli-Kovacic, a general practitioner, had a vital role in this example of Mljet. After working many years on the island, she had the opportunity to become individually acquainted with each patient, and so she greatly assisted in raising their awareness with regard to the research. In this respect, the leaders and the heads of the local community also assisted this research. Of equal importance is the feedback where patients are informed on their role in the research, and on the results that have emerged on the basis of their participation. In as much as stigmatization is on the path of being transformed into a positive value, so are patients on the path of being transformed into key praiseworthy individuals through their contributions.

Conclusions

Mal de Meleda and leprosy are two different diseases; yet, they are linked by a common form of stigmatization rooted in the collective memory of the population of the Mljet island. As a result of recently conducted genetic research, it has been confirmed that one of the central reasons for the same form of stigmatization lies precisely in the fact that in the past Mljet was an isolation site for people diagnosed with leprosy. In its essence, mechanisms of perception of Mal de Meleda imitate mechanisms of behavior and perception of the leprosy within the population, manifested in patients' self-isolation and their withdrawal from treatment and research. To combat the stereotyped stigma a highly ethical and knowledgeable approach might be useful.

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