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Emergence of pediatric rare diseases

Review of present policies and opportunities for improvement

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Abbreviations: UCLA, University of California Los Angeles

In this article we discuss the steps taken by the United States (US) and the European Union (EU) to meet the health care needs of children with rare diseases and suggest possible directions for future endeavors for further improvement. We reviewed 23 reports and nine legislative documents related to pediatric rare diseases and public policy. We assessed the outcome measures of access and satisfaction with medical services by utilizing the surveys done by the European Organization for Rare Diseases -Eurordis (n = 5,963). Comparable surveys were not available in the US. Our analyses of the existing policies and surveys indicate multiple differences between the US and EU. While the US policies seem to be aimed at disease diagnosis and neonatal screening, EU legislators appear to be focusing on access to existing specialized care. However, both systems have struggled with effectively promoting new treatments. Also, while Eurordis surveys have evaluated areas such as the access to medical services, access to social services and satisfaction with the services received in Europe, there are no comparable surveys in the United States. We conclude that better tools are needed to measure the quality of care, needs-assessment and outcome of pediatric rare diseases in both the EU and US. We suggest a better assessment of areas such as access to primary and specialty care, legal advocacy, comfort-care, end-of-life care, social and financial services, psychological support and quality outcome-measures.

Introduction

Pediatric rare diseases have received increased attention in recent years due to greater public awareness, significantly improved understanding and treatment of the relatively more common disorders, elimination of nutritional deficiencies and the development of laws related to the treatment of rare diseases.[1-4] Although some advances have been made in this area, pediatric rare diseases are still a large medical, social and economic issue in the United States (US) and the European Union (EU) and additional work remains to be done to overcome the burdens these diseases place on our healthcare system and communities.[1,5]

A disease is considered rare when it affects less than 200,000 individuals in the US or less than one in 2,000 people in Europe.[6] Although each individual disease affects a small percentage of the population, with over 6,800 rare diseases discovered, the aggregate number of affected individuals sums up to 8% of the population, affecting an estimated 25 million people in the US and nearly 30 million in Europe.[6,7] These rare diseases are 80% genetic in nature, with the inherent problems of limited resources, lack of research, scarce expertise and patients that are few in number and geographically spread.[6,7] Very few studies have addressed the needs of the pediatric population with rare diseases separately from that of adults. However, since nearly 50 to 75 percent of rare diseases begin in childhood, these pediatric disorders deserve special priority.[7]

In this report we assess the steps taken by the United States and the European Union (EU) in order to highlight the opportunities for improvement and future endeavors.

Public Policy and Rare Diseases

Establishing rare diseases as a public health priority. Public policy toward rare diseases in both the United States and Europe was initially pioneered by patient support groups working toward search for cures and better management of individual diseases.[7] In the United States, patients with rare diseases had limited hope for treatments due to inadequate market incentives for the pharmaceutical industry to develop these "orphan drugs." In the 1970s, the National Organization for Rare Disorders (NORD), a private organization, pushed for legislation in the development of orphan drugs that led to the Orphan Drug Act issued in 1983. This act provides tax benefits, grants for testing and market exclusivity of treatments.[8] The Office of Rare Diseases Research (ORDR) was

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created in 1993 within the office of the director of the National Institutes of Health (NIH) to stimulate and coordinate research on rare diseases and to support research that responds to the needs of patients with rare diseases. This office gained statutory authorization on November 6, 2002 through the Rare Diseases Act of 2002, Public Law 107–280.[9]

In France, the Association Française contre les Myopathies (AFM) was created in 1958 by a group of patients and their families to cure neuromuscular diseases and reduce the disabilities that they cause.[10] In April 1999, this concept was expanded when the European Parliament and the Council of the European Union adopted a program of community action on rare diseases. The goal of this program was to improve the quality of life for affected individuals, facilitating access to information for the patients and their families and supporting transnational cooperation between voluntary and professional support groups.[11] In September of 2003, the focus on rare diseases was established as a public health priority when the European Parliament and Council adopted a new six-year community action program.[12] In October 2007, a second five-year program was established to reduce the occurrence of rare diseases and in June 2009, the European Commission adopted a proposal on rare diseases that marked the culmination of a series of legislative acts allowing for recognition of rare diseases as a public health priority, requiring community action.[13-15]

Policy Goals

Patient centered care. In the US, the American Academy of Pediatrics has developed a medical home model for delivering primary care that is accessible, comprehensive and family-centered for all children, including those with special health care needs. It provides a forum to coordinate specialty care, educational services, home care, family support and other public and community services essential for both the patients and their families.[16] Also in the US, over 1,000 individual patient- and parent-run support groups for rare genetic disorders are networked together under the umbrella of the Genetic Alliance (*http://www.geneticalliance.org/*).

Similarly, the EU has focused on improving access to patient care, along with improving the quality of care, and the information and social services provided for the affected individuals, through the Rare Disease Patient Solidarity Project (RAPSODY).[17] Under the Eurordis mandate, another project called "Rare! Together" was created to encourage existing patient networks to become well-structured disease-specific federations at the European level.[18] The European approach has thus involved empowering patients and existing patient networks in providing services.

Identification of specialized health care centers. In the US, presently there is no unified designation throughout the country for the hospitals and medical groups that are equipped and adequately staffed with the physicians and ancillary services experienced in caring for children afflicted with rare diseases. However, each state has its unique designation for such hospitals. As an example, in the state of California, the Department of Health Care Services has identified "Special Care Centers" that provide comprehensive multi-disciplinary care that is coordinated through California Children's Services (CCS) and Genetically Handicapped Persons Program (GHPP).[19] Hence, academic centers and children's hospitals are often a natural referral choice in most states.

The EU approach is based on providing standardized systems of care through "Centres of Reference" and "Centres of Excellence." The aforementioned designation is meant to identify medical facilities that are designed to offer the expertise and services needed to treat rare and complex diseases.[20,21] Currently, efforts are being made to enhance communication between these Centres of Excellence through European networks.[22]

Research into diagnosis of rare diseases. In the United States there has been a great deal of emphasis on using research to help determine the genetic origin of rare diseases which are responsible for 80% of these disorders. The Rare Diseases Clinical Research Network (RDCRN), established initially by the NIH in 2002, now consists of 19 research consortia studying approximately 90 rare diseases at 97 academic institutions and a central Data and Technology Coordinating Center (DTCC) for data collection and sharing.[23] The consortia enable researchers from different centers and disciplines to collaborate in conducting clinical research studies. Early genetic testing in the form of a newborn screening program has created the potential for early diagnosis of rare diseases, which may lead to more effective interventions and reduction of recurrence rate through parental counseling.[24] Because the "market" for testing of each individual rare disease is very small, large academic and commercial clinical laboratories are not interested in addressing them, as the cost to set up and validate the test would likely be much higher than any expected return from actual patient testing. To make novel genetic tests more available to the patients and families with rare diseases, the Office of Rare Diseases, in collaboration with the NIH and other Federal organizations, has fostered the establishment of a network of Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories that have agreed to specialize in the delivery of these esoteric services. The effort was administered by funding through the CETT (Collaboration, Education and Test Translation) program to facilitate the translation of genetic tests from research laboratories to clinical practice.[9,25] Capable laboratories were invited to submit proposals for development of one or more rare-disease genetic tests not currently available in any CLIA-certified laboratory. Level of support was determined based on clinical need, collaboration with a research laboratory expert in the particular disease and difficulty of working with the relevant disease gene. The program was successful in jump-starting and bringing together a network of laboratories interested in testing for rare diseases, which have since continued to increase their test "menus" independently.

Development of orphan drugs. In the US, the passing of the Orphan Drug Act has provided a financial incentive for the research and production of orphan drugs leading to 300 orphan drugs approved and marketed and over 800 additional drugs in the research process.[26-29] In 2009, ORDR established the

Therapeutics for Rare and Neglected Diseases (TRND) program to reduce risk for developing drugs to meet FDA requirements and to work with NIH for accelerated development of orphan products.[30]

In the EU, the Committee for Orphan Medicinal Products (COMP), established in 2000, has led to more than 40 new products by 2007 and more than 500 undergoing clinical tests.[21] The Rare Disease Task Force (RDTF), set up in January 2004, works to advise and assist the Directorate in promoting the optimal prevention, diagnosis and treatment of rare diseases in Europe, and provides a forum for discussion on issues related to rare diseases.[22]

Policy Outcome

United States. In the United States, there have been no national surveys aimed specifically at children with rare diseases. Between the years 2005–2006, an extensive survey was performed by the Centers for Disease Control and Prevention (CDC) on close to 39,000 Children with Special Health Care Needs (CSHCN).[31] These children are defined by the federal Maternal and Child Health Bureau to be those who have or are at increased risk for a chronic physical, developmental, behavioral, or emotional condition and who also require health care services beyond those required by children generally.[32] Although children with rare diseases qualify as CSHCN, children with common chronic diseases such as asthma and diabetes comprise an overwhelming majority of the individuals in this survey. Therefore, the results of this study were not deemed as specifically reflective of the needs of children with rare diseases, nor are there any other studies available that assess the needs of this population in the US.

European Union. In the European Union, there were a series of EurordisCare surveys conducted by the European Organization for Rare Diseases (Eurordis) as part of the RAPSODY project. The *EurordisCare 1* survey was conducted in 2003 to compare health care by focusing on six diseases in 17 countries.[33] In 2004, the *EurordisCare 2* surveyed eight diseases to find reasons for diagnostic delays leading to late treatments and disease progression.[34] The *EurordisCare 3* Survey in 2007 was designed to advise the European Centres of Reference, surveying patients' experiences and expectations concerning access to health services for 16 rare diseases in 23 different countries in Europe. The number of respondents to the latest survey is 5,963 patients with rare diseases.[35] The findings of the surveys indicate that patients with rare diseases expect the specialized centers to provide them with adequate knowledge of the disease, a multidisciplinary approach to care, adequate sharing of information between health professionals and patients and integrating medical care with social services. In the EU, lack of recognition through appropriate coding and classification systems and misdiagnosis or non-diagnosis of rare diseases were the biggest reported obstacles toward improving the quality of life. Access to the eight most needed medical services was reported as difficult or impossible in 26% of the cases. For patients reporting that access was impossible (11%), lack of referral (69%) was the most prevalent reason, followed by the unavailability of services (52%) and waiting time (41%).[35,36] Approximately 50% of the patients reported satisfaction with "the most needed medical services."[35] However, these surveys highlight the gaps in the availability of social services for patients with rare diseases. In the EU, 32% of patients said that it was difficult or impossible to access social assistance and, at times, the patients waited more than five years to get access to social services.[37]

Discussion

The American Academy of Pediatrics issued a policy statement in October 2003 mandating equal rights to comprehensive health care that is fully portable and ensures continuous coverage for all children.[37] They mention that chronically ill children should be recognized to have special needs requiring appropriate reimbursement of their evaluation and treatment, care coordination, case management, team collaboration and medically indicated interventions and surgeries. The US and member countries of the EU have taken on the task of addressing the health care needs of these patients.

The available data suggest that the US health-related policies have focused on the diagnosis of these diseases by concentrating on research, improving access to credible laboratories, newborn screening and facilitating a coordinated research effort. However, there is no uniform special designation for the hospitals and medical groups that are equipped and adequately staffed with the physicians and ancillary services experienced in caring for children with rare diseases. It is therefore the patients and their physicians who search and make a referral to the institutions deemed as qualified in caring for these children. Academic centers and children's hospitals that perform research and can deal with the high cost and lower reimbursement rates are often a natural choice for such referrals. Therefore, many patients and their families find themselves traveling long distances away from their community to get appropriate care.

On the other hand, the EU policy makers have concentrated their resources on providing access to the existing technology by facilitating the availability of qualified centers that may provide specialized care to these patients. As the surveys mentioned above indicate, these two approaches each fall short of fully assessing or meeting the needs of these children and their families in certain areas.

Clearly, improved access to medical-home and transition care, along with improved availability of social services can improve the existing care of all patients, regardless of their diagnosis. However, with the escalating cost of health care and the global economic downturn, prioritization of the resources has become an increasingly vital issue. It is therefore empiric for health care providers and policy makers to identify the interventions that have the greatest positive impact on the life and wellbeing of these patients.

While the existing reports are a good starting point, creation of a questionnaire tailored toward pediatric rare diseases may better provide the information needed for future directions. A coordinated effort between the US and EU researchers and policy makers may lead to a more uniform needs-assessment tool with outcome-measures that can in turn direct us toward the

best approach in treating these children. We suggest that possible future needs-assessment questionnaires include such topics as access to family centered medical-home where patients and their families are able to make informed decisions and access to comfort and palliative care that includes, but is not limited to, pain and symptom management that starts at the time of diagnosis. As the patient responses to the previous surveys mentioned above suggest, access to primary and specialty care, social services, legal advocacy and psychological support should be longitudinally assessed. Furthermore, addition of questions dealing with the direct and indirect financial burden of disease can help policy-makers devise global cost saving measures that do not simply shift the cost onto these families.

The most obvious, yet challenging, measure of any treatment and health-policy intervention is the assessment of the individuals' health and productivity outcomes. Some of the more meaningful outcome measures may begin with the quantification of the "diagnostic odyssey" or the time required to diagnose a certain disease in the affected patient. This process can extend over many years, incurring tremendous financial and emotional costs on the family and society. The CETT program in the US, mentioned above, addressed this dilemma by making available clinical tests for rare diseases that were formerly nonexistent or available only in research settings. More recently, the advent of "next-generation" DNA sequencing is enabling rare disease diagnosis via genome-wide analysis as opposed to the traditional single-gene-targeted methods, in many cases putting a conclusive end to the diagnostic odyssey in far less time and expense.[38]

Assessment of school function that includes age-appropriate academic and social success may be a good measure of the children's health, while assessing successful transition to adulthood through the acquisition of the skills needed to lead an independent life and meaningful relationships with cohorts is a more appropriate outcome measure in teens and young adults. Furthermore, productivity in adults can be determined by the ability to achieve partial or complete financial independence. Finally, to assess the overall quality of life, outcome measures may include a self-assessed sense of well-being by the patients and their families.

Conclusion

To further study and compare the two systems, we need to have better comparative tools to measure the quality of care, needs assessment and outcome in both the US and EU. The health care systems in the United States and the European Union are structured differently, but share common goals. The burden of rare diseases is quite real and, with expanding knowledge and emerging technology, it is our duty to provide appropriate care to these patients. The management and care provided to children will determine their present and future quality of life. Increased recognition of rare diseases by other nations such as Japan, Australia, Russia and Canada is an encouraging sign of a possible trend in addressing rare diseases. Ultimately, as the countries with emerging economies succeed in eliminating malnutrition and resolve the more common diseases, they can join in this effort. Since some of these nations have a higher birth rate and population than the economically developed countries, they provide a rare opportunity where experience and technology of the partnering countries coupled with the cumulatively vast population of these nations can provide an ideal setting for improved health care and advancement of medicine.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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