RARE DISEASES AND ORPHAN DRUGS

An International Journal of Public Health

2015
Volume 2, Number 3
Print ISSN 2284-2543
Online ISSN 2385-2364

Publisher
Istituto Superiore di Sanità

RARE DISEASES AND ORPHAN DRUGS
An International Journal of Public Health

Publisher
Istituto Superiore di Sanità
Legal representative of the Istituto Superiore di Sanità Gualtiero Ricciardi
Reg. Stampa Tribunale di Roma, n. 35/14, 10 marzo 2014
Print ISSN 2284-2543,
Online ISSN 2385-2364

Publishing support
Il Pensiero Scientifico Editore, Rome

Contacts
RARE Journal Secretariat
National Centre for Rare Diseases
Istituto Superiore di Sanità (ISS)
Viale Regina Elena 299
00161 Rome, Italy

Email secretariat@rarejournal.org
http://rarejournal.org/

Rare Disease and Orphan Drugs
is published three times a year and in special issues.

Papers to be presented for publication should be submitted online to http://rarejournal.org/

The Rare Diseases and Orphan Drugs Journal has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under Grant Agreement n. 305690: RARE-Bestpractices project: **www.rarebestpractices.eu**. Sole responsibility lies with the authors and the European Commission is not responsible for any use that may be made of the information contained therein.

RARE DISEASES AND ORPHAN DRUGS
An International Journal of Public Health

2015
Volume 2, Number 3

Contents

The Rare Diseases and Orphan Drugs Journal has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under Grant Agreement n. 305690: RARE-Bestpractices project: **www.rarebestpractices.eu**. Sole responsibility lies with the authors and the European Commission is not responsible for any use that may be made of the information contained therein.

Review Article

Shared decision-making in rare diseases: an overview

Jeanette Pérez-Ramos[1,2], Analía Abt-Sacks[1,2], Lilisbeth Perestelo-Pérez[2,3,4], Amado Rivero-Santana[1,2], Ana Toledo-Chávarri[1,2], Nerea González[2,5], Pedro Serrano-Aguilar[2,3,4]

[1]Canary Islands Foundation of Health Research (FUNCANIS), Tenerife, Spain
[2]Health Services Research on Chronic Patients Network (REDISSEC), Spain
[3]Evaluation Unit of the Canary Islands Health Service (SESCS), Tenerife, Spain
[4]Center for Biomedical Research of the Canary Islands (CIBICAN), Tenerife, Spain
[5]Research Unit, Hospital Galdakao-Usansolo, Basque Country, Spain

Open access

Correspondence to
Jeanette Pérez-Ramos, MPsych, Phd
Servicio de Evaluación y Planificación
Dirección del Servicio Canario de la Salud
Centro de Salud El Chorrillo
Camino Candelaria, 44
CP 38109 El Rosario
S/C de Tenerife, España
Tel +34 922 684019 (ext 241)
E-mail: jpramos@sescs.es
jeanettepsico@gmail.com

Competing interest
None declared

Received: 9 December, 2015
Accepted: 9 February, 2016

The Rare Diseases and Orphan Drugs Journal has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under Grant Agreement n. 305690 RARE-Bestpractices project www.rarebestpractices.eu.
Sole responsibility lies with the authors and the European Commission is not responsible for any use that may be made of the information contained therein.

Abstract

Patients with rare diseases often face difficulties in clinical care due to the low prevalence of their diseases and the resulting healthcare providers' lack of expertise. Valid and standardized guidelines for clinical management are also lacking due to the scarcity of research and the variability of the clinical expressivity within each disease. Clinical decision-making in an uncertainty context should take advantage of involving patients in deeper informational process to promote valid shared decision-making between patients/caregivers and healthcare professionals. This process of patient/caregiver empowerment is a priority in the context of rare diseases, as it encourages acquisition of information that will help improving patient-healthcare professional's interaction, and building a collaborative relationship. It is also a chance for healthcare professionals to learn about rare diseases from the perspective of patients.
The aim of this article is to conduct an overview of existing studies focused on promoting patients/caregivers empowerment and shared decision-making (using or not decision aids) in the area of rare diseases.

Key words

Caregivers, decision aids, empowerment, patients, rare diseases, shared decision-making.

Background

Rare diseases (RDs) are defined in Europe as chronic life-threatening or debilitating conditions affecting no more than 5 in 10,000 people, characterized by difficulties in diagnosing and, for most of them, by having no effective therapy [1]. Though the accurate incidence and prevalence of most RDs are still unknown [2], their low magnitudes limits both the growth of clinical experience and research activities to improve the availability of valid knowledge on diagnostic and therapeutic procedures [3]. Besides, different constraints to research in RDs such as funding limitations, limited commercial interest and logistic barriers for patient recruitment and engagement have also contributed to the gap of valid scientific knowledge [4]. Additional limitations are the regulatory burdens, fragmented infrastructure, inconsistent databases, and the lack of proper communication between researchers, healthcare professionals, and patients [5].

All these circumstances, together with the scarcity and limited effectiveness of available diagnostic and therapeutic tools, maintain a high uncertainty and anxiety among healthcare professionals, patients and families, explaining the existing rates of errors and delays to get an appropriate diagnosis and treatment [6]. Because often there is not a single or 'best' option based on scientific evidence, it is necessary to inform patients and incorporate their values and preferences in the process of decision-making [7]. In this context, patient and caregiver empowerment and participation in decision-making along their care processes became an important aspect to improve the quality of healthcare in RDs.

Empowerment of people affected by RDs is relevant to support effective participation in decision-making along the interaction with healthcare professionals mainly when diagnostic or therapeutic options are complex or supported by limited evidence of efficacy and/or safety. At individual level, the term 'empowerment' involves

an assessment of one's knowledge and learning acquired through the personal experience of living with the disease, in addition to the knowledge acquired from biomedical sources. It also encompasses action toward self-management of the disease, which requires creating the necessary capabilities. Empowerment of patients and their organizations are one of the main aims of the European Council Recommendation in the field of RDs (2009/C151/02), and World Health Organization (Statement 2010), considering it an essential concept of health promotion and disease management.

In this sense, the RARE-Bestpractices project (www.rarebestpractices.eu) is developing a platform to enhance clinical management and to reduce healthcare inequalities for RDs patients by improving the exchange of knowledge and reliable information on RDs. The European Commission (European Union Seventh Framework Programme) funded this four-year study (until December 2016) and its main goal is to promote communication on the management of RDs. It provides mechanisms to identify and prioritize clinical RDs research needs, taking into consideration both patients' and healthcare professionals' needs and interests. In addition, it addresses patients' and caregivers' demand for updated and evidence-based clinical practice guidelines on RDs [8-10], and facilitates timely, effective and efficient translation of research results for general audiences and patients.

Other actions from the European Commission also increase patient involvement in research as active contributors on decision-making, not just as cases of study [11]. The access of patients with capacity to make decisions to the Committee for Orphan Medicinal Products, or the creation of a working group with patient representatives in response to the first European Union Public Health Programme (2003-2008) are some examples. The participation of patient organizations in research [12-14] or the incorporation of patients' perspective in the study designs [15-18] is also noteworthy.

Despite the advances described, neither the healthcare systems nor the healthcare professional organizations in the European Union are doing clear or powerful efforts to inform, sensitize and train healthcare professionals to work with patients in a needed scenario of informed and participatory decision-making. This report provides an overview of the literature to identify published studies focused on promoting empowerment of RDs patients/caregivers and shared decision-making in the clinical encounter, either evaluating basic variables for its implementation or using specific decision aids.

Shared decision-making and patient decision aids

Promoting patient participation in healthcare is considered an ethical imperative, and the Salzburg Declaration [19] states it, where healthcare professionals and patients are invited to become co-responsible for healthcare management. The 'Shared Decision-Making' model (SDM) [20] involves a two way process where the healthcare professional provides the technical expertise and the patient brings their values, preferences and concerns regarding the interventions to choose [21]. The mutual exchange of information and acceptance of the decision may not occur in other decision models, such as the paternalistic or informed models; however, this aspect is a prerequisite for SDM, although mutual acceptance does not always indicate the existence of a SDM [22]. In the paternalistic model, patients play a passive role. Then, physicians suppose that they know the best option to choose in the decisional process and inform patients about it, although they must give their informed consent. In the informed model, information exchange is also from physicians to patients, but the decision is taken by patients alone, needing the physician's agreement to implement the preferred choice [23].

To support the SDM process, patient decision aids (PtDAs) have been developed [24]. They are instruments that help make specific and deliberate decisions, providing information about the available options and their expected results. PtDAs can be presented in different formats (print, video, CD-ROM, Web) and with different levels of informative detail, but they always include information on the potential risks and benefits of each option [25, 26]. These tools differ from educational materials and the informed consent to the extent that they help elicit patients' preferences and values regarding the different options. They can be used during or outside consultation but, although they represent a facilitator of communication between patients and healthcare professionals in the clinical encounter, they must not be considered as a substitute of professionals' advice. PtDAs are useful in very specific contexts, such as RDs, where many healthcare professionals may lack the necessary knowledge about the therapeutic options and their effects. Thus, having PtDAs might guarantee the access of patients, families and professionals to scientifically valid and adapted information to promote SDM [22].

Currently a PtDAs inventory with more than 600 tools is available, of which more than a half are accessible on the Ottawa Health Research Institute's website (https://decisionaid.ohri.ca/). Academic institutions have developed some of these PtDAs, whereas others have been created by organizations that are specialized in the dissemination of healthcare information. Some of the main institutions devoted to the development and assessment of PtDAs are Healthwise/Informed Medical Decisions Foundation (www.healthwise.org; www.imdfoundation.org), Knowledge and Encounter Research Unit (Mayo Clinic) (http://www.mayo.edu/research/labs/knowledge-evaluation-research-unit) or Cardiff University (Decision Laboratory: www.decisionlaboratory.com).

Owing to the large variability of available PtDAs for dif-

ferent medical conditions, the International Patient Decision Aids Standards (www.ipdas.ohri.ca) were established to assess the quality of these tools taking into account three dimensions: content, development process and effectiveness assessment [27]. To establish the effectiveness of PtDAs it is necesary to evaluate the characteristics and quality of the decision-making process and the quality of the choice made [28]. In the first case, measures should explore if PtDAs help patients to: a) recognize that a decision needs to be made; 2) feel informed about the options (including risks, benefits, and consequences); 3) be clear about what matters most to them; 4) discuss goals, concerns, and preferences with their healthcare professionals; 5) be involved in decision-making. Considering the quality of the final choice implies to evaluate the extent to which patients are informed and receive treatments that are concordant with their goals and treatment preferences. In this sense, is useful to measure the patient's understanding of the information and the use of exercises to elicit preferences.

Clinical trials assessing the effectiveness of these tools versus standard practice have shown that PtDAs increase patients' knowledge, the proportion of people with accurate risk perceptions, the proportion of patients choosing an option congruent with their values, reducing decisional conflict related to feeling uninformed and feeling unclear about personal values, as well as the proportion of people who were passive in decision-making and who remained undecided post-intervention. PtDAs have also a positive effect on patient-healthcare professional communication, increasing the satisfaction with the decision-making process. It has also been observed that when patients are adequately informed about different therapeutic procedures with comparable effectiveness, they tend to choose the least invasive procedures and tend to start treatment earlier [25].

Empirical evidence for shared decision-making in rare diseases

Empirical studies about SDM or PtDAs interventions are still very scarce in the field of RDs. Hossler et al [29], in a pre-post uncontrolled study, analysed the acceptability of an interactive computerized decision aid to help engage patients with amyotrophic lateral sclerosis (ALS) in effective advance care planning. ALS patients perceived quantity and quality of information very positively, as it was the overall satisfaction with the PtDA and its accuracy in reflecting patients' wishes. The intervention prompted patients to discuss advance care planning with their families and to share their advance care directives generated by the software with their physicians. In other study, De Abreu et al [30] assessed the responses of patients with lupus nephritis and their physicians to a PtDA describing the treatment options and their potential benefits and risks. A significantly higher rate of physicians selected oral treatment options (96% vs 68%, $p < 0.001$). Decision justification was different for patients and clinicians in each group; risk of side effects and the risk/benefit trade-offs were more relevant for physicians, whereas risk potential and absence of prior joint involvement were the variables that predicted patients' choice of the oral option. Finally, Yazdani et al [31] published the preliminary results (meta-analyses of effectiveness results and focus groups) of the development of a PtDA for racial/ethnic minorities with lupus nephritis. The use of this tool is expected to facilitate patient-centred care in these cases.

In addition, some qualitative studies explored patients' views about SDM and their involvement in healthcare. Hanneman-Weber et al [32] published a multi-level empirical study protocol that uses a three phases' mixed method. The aim of the study was to assess the contribution of communication processes and SDM among healthcare teams, in order to improve the satisfaction of patients affected by ALS, Marfan's syndrome, Wilson's disease, epidermolysis bullosa, Duchenne muscular dystrophy, and neurodegeneration with brain iron accumulation. A year later, the first results were also published [33], analysing interaction experiences among 107 patients affected by the six mentioned RDs. Using semi-structured interviews, four interaction patterns were identified: paternalistic, collaborative, led by the patient and confrontational. This analysis also showed that professionals' lack of knowledge becomes a handicap that creates uncertainty and dissent within the highly specialized treatment process that any RD demands. In such cases, the patient becomes the expert in a way that he may lead the interaction with the professional. Regarding the willingness to change roles, this research and others suggest a higher resistance to SDM from professionals than from patients [34].

Patient satisfaction with the healthcare system might be a relevant variable for an adequate implementation of SDM in the field of RDs. Despite some studies provide information on expectations and satisfaction with healthcare services by patients affected by ALS [35, 36], there is a lack of valid knowledge explaining the basic psychosocial processes which support the way in which people with RDs cooperate or get involved with the healthcare providers. The systematic review carried out by Foley et al [37] concluded that ALS patients are often dissatisfied with healthcare services and have unmet expectations of their care. In order to shed light on this knowledge gap, a subsequent study by the same author [38] carried out in-depth interviews with 34 people affected by ALS, reporting that older participants had a wider acceptance of the disease and the idea of death than young or middle-aged patients. This study also observed that families play a relevant role in participants' commitment to healthcare services, as well as in decisions taken at different stages of life.

Discussion and conclusions

People with RDs, their caregivers and support organizations are among the groups with the greatest activity within the healthcare sector, mainly because of their own struggle looking for acknowledgement and answers that may improve their healthcare. Thus, it is crucial that health policy makers and professionals acknowledge the active and collaborative role of these groups, fostering SDM during the clinical process. Yet providing patients with a certain level of control to approach their disease might call for a change in traditional roles in healthcare services, as well as having adapted materials available to the users.

According to the revised literature, the field of RDs is indeed expanding, indicating political and social acknowledgement towards research and resources development that empower the patients involved. Nevertheless, despite studies that highlight the contribution of patients´ organizations and explore outcome measures that are essential for an adequate implementation of SDM, no specific PtDAs have been designed so far. Because of the available scientific evidence about the effectiveness of these tools, especially in the uncertain context that surrounds RDs, it is advisable to allocate resources to design and assess these PtDAs.

Recognition of the need of valid, reliable and accessible educational materials also requires designing, developing and assessing specific PtDAs for RDs, focused on the SDM between healthcare professionals and patients. The European Commission is promoting virtual communities or the provision of resources that support patient empowerment and shared decision-making. In this sense, the RareConnect project (www.rareconnect.org) gives support to patients´ communities with specific RDs, and has moderators that supervise the uploaded contents on the website. Other projects, such as the EURORDIS Summer School, offer face to face training programmes, but also offer access to freely available on-line modules, webcasts and slide presentations (www.eurordis.org).

In Europe, some webs could become a valid option to host informative resources and PtDAs. Orphanet (www.orpha.net) offers information about several RDs, available treatments and experts location. PatientsLikeMe (www.patientslikeme.com) is another example of health data-sharing platform where patients can share and learn from their experiences and outcome-based health data, and aligning patient and industry interests through data-sharing partnerships. Likewise, the web platform PyDeSalud (www.pydesalud.com), though currently deals mainly with high prevalence diseases, is also planning the development of PtDAs for Spanish speakers people affected by RDs. This website, whose contents are obtained from rigorous research and are supervised by a scientific experts committee, promotes the exchange of informative material which facilitate SDM and PtDAs. It also contains patients' experiences and encourages the participation of expert patients in determining and prioritizing research needs in healthcare agendas. In this way, narrative based medicine [39] helps SDM, acting as a bridge between the clinical knowledge of the physician and the patients' subjective experiences, and supporting the various stakeholders toward the improvement of knowledge and the shared management of the disease [40].

Consequently, PtDAs are expected to reduce the current level of uncertainty at the same time that support SDM, lightening the difficulties due to the lack of specialization required in the medical encounter with patients affected by RDs. Additionally, the creation of virtual communities of practice which host shared experiences coming both from clinical practice and patients, may contribute to improve the clinical and therapeutic data of this group of diseases [41].

In conclusion, it is advisable to increase support for actions aiming at the empowerment of people affected by RDs and their organizations, as well as allocating resources for research in SDM and the creation of PtDAs targeting these patients.

References

1. Taruscio D, Gentile AE, Evangelista T, Frazzica RG, Bushby K, Montserrat AM. Centres of Expertise and European Reference Networks: key issues in the field of rare diseases. The EUCERD Recommendations. Blood Transfus 2014;12(3):s621-5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4044812/
2. Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions on Rare Diseases: Europes' Challenges, (2009/C 151/02). Available from: http://ec.europa.eu/health/rare_diseases/docs/2014_rarediseases_implementationreport_en.pdf
3. Griggs RC, Batshaw M, Dunkle M, Gopal-Srivastava R, Kaye E, Krischer J, et al. Clinical research for rare disease: opportunities, challenges, and solutions. Mol Genet Metab 2009;96(1):20-6. doi: 10.1016/j.ymgme.2008.10.003
4. Gagne J, Thompson L, O'Keefe K, Kesselheim A. Innovative research methods for studying treatments for rare diseases: methodological review. BMJ 2014;349:g6802. doi: http://dx.doi.org/10.1136/bmj.g6802
5. Légaré F, Ratté S, Gravel K, Graham ID. Barriers and facilitators to implementing shared decision-making in clinical practice: update of a systematic review of health professionals' perceptions. Patient Educ Couns 2008;73(3):526-35. doi: 10.1016/j.pec.2008.07.018
6. Faurisson F. Survey of the delay in diagnosis for 8 rare diseases in Europe: EurordisCare2. Available from: http://www.eurordis.org/IMG/pdf/Fact_Sheet_Eurordiscare2.pdf
7. Weston WW. Informed and shared decision-making: the crux of patient-centred care. CMAJ 2001;165(4):438-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC81370/
8. Taruscio D, Morciano C, Laricchiuta P, Mincarone P, Palazzo F, Leo CG, et al. RARE-Bestpractices: a platform for sharing best practices for the management of rare diseases. Rare Dis Orphan Drugs 2014;1(1):5-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4249596/
9. Hilton-Boon M, Ritchie K, Manson J, Taruscio D, Auld J, Uk J, et al. Improving the retrieval and dissemination of rare

disease guidelines and research recommendations: a RARE-Bestpractices initiative. Rare Dis Orphan Drugs 2014;1(1):20-9. Available from: http://rarejournal.org/rarejournal/article/view/33

10. Sejersen T, Del Giovane C, Filippini G, Leo CG, Meerpohl JJ, Mincarone P, et al. Methodology for production of best practice guidelines for rare diseases. Rare Dis Orphan Drugs 2014;1(1):10-9.
11. Marcus AD. Patients with rare diseases work to jump-start research; advocacy groups create their own tissue banks to aid in drug treatment. Wall Street Journal (East Ed) 2006;11:D1, D2. Available from: http://www.wsj.com/articles/SB115257685637802872
12. Barr PJ, Scholl I, Bravo P, Faber MJ, Elwyn G, McAllister M. Assessment of patient empowerment: a systematic review of measures. PLoS ONE 2015;10(5):e0126553. doi: 10.1371/journal.pone.0126553
13. Bravo P, Edwards A, Barr PJ, Scholl I, Elwyn G, McAllister M, the Cochrane Healthcare Quality Research Group, Cardiff University. Conceptualising patient empowerment: a mixed methods study. BMC Health Serv Res 2015;15:252. Available from: http://www.biomedcentral.com/1472-6963/15/252
14. Linertová R, Serrano-Aguilar P, Posada-de-la-Paz M, Hens-Pérez M, Kanavos P, Taruscio D, et al. Delphi approach to select rare diseases for a European representative survey. The BURQOL-RD study. Health Policy 2012;108(1):19-26. doi: 10.1016/j.healthpol.2012.08.001
15. Serrano-Aguilar P, Trujillo-Martin MDM, Pérez de la Rosa A, Cuellar-Pompa L, Saavedra-Medina H, Linertova R, et al. Patient participation in a clinical guideline development for systemic lupus erythematosus. Patient Educ Couns 2015;98(9):1156-63. doi: http://dx.doi.org/10.1016/j.pec.2015.05.022
16. Serrano-Aguilar P, Trujillo-Martín MM, Ramos-Goñi JM, Mahtani-Chugani V, Perestelo-Pérez L, Posada-de la Paz M. Patient involvement in health research: a contribution to a systematic review on the effectiveness of treatments for degenerative ataxias. Soc Sci Med 2009;69(6):920-5. doi: 10.1016/j.socscimed.2009.07.005.
17. Caron-Flinterman JF, Broerse JE, Bunders JF. The experiential knowledge of patients: a new resource for biomedical research? Soc Sci Med 2005;60: 2575-84. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15814182
18. Crawford MJ, Rutter D, Manley C, Weaver T, Bhui K, Fulop N, et al. Systematic review of involving patients in the planning and development of health care. BMJ 2002;325:1263-67. Available from: http://www.ncbi.nlm.nih.gov/pubmed/12458240
19. Salzburg statement on shared decision making. BMJ 2011;342:d1745. doi: http://dx.doi.org/10.1136/bmj.d1745
20. Braddock CH. The emerging importance and relevance of shared decision making to clinical practice. Med Decis Making 2010;30(5):5S-7S. doi: 10.1177/0272989X10381344
21. Gafni A, Charles C, Whelan T. The physician-patient encounter: the physician as a perfect agent for the patient versus the informed treatment decision-making model. Soc Sci Med 1998;47(3):347-54.
22. Joseph-Williams N, Elwyn G, Edwards A. Knowledge is not power for patients: a systematic review and thematic synthesis of patient-reported barriers and facilitators to shared decision making. Patient Educ Couns 2014;94(3):291-309. doi: 10.1016/j.pec.2013.10.031
23. Charles C, Gafni A, Whelan T. Decision-making in the physician-patient encounter: revisiting the shared treatment decision-making model. Soc Sci Med 1999; 49(5):651-661. http://www.ncbi.nlm.nih.gov/pubmed/10452420
24. Coulter A, Stilwell D, Kryworuchko J, Mullen PD, Jenn C, van der Weijden T. A systematic development process for patient decision aids. BMC Med Inform Decis Mak 2013;13(Suppl 2):S2. doi: 10.1186/1472-6947-13-S2-S2
25. Stacey D, Légaré F, Col NF, Bennett CL, Barry MJ, Eden KB, et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database Syst Rev 2014; 1:CD001431. Available from: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD001431/abstract;jsessionid=B7B4B25864312A510DC3749B0BCFA651.f02t03
26. Elwyn G, Frosch D, Rollnick S. Dual equipoise shared decision making: definitions for decision and behaviour support interventions. Implement Sci 2009;4:75. doi:10.1186/1748-5908-4-75
27. Elwyn G, O'Connor A, Stacey D, Volk R, Edwards A, Coulter A, et al. Developing a quality criteria framework for patient decision aids: online international Delphi consensus process. BMJ 2006;333:417. doi: http://dx.doi.org/10.1136/bmj.38926.629329.AE
28. Sepucha K, Borkhoff C, Lally J, Levin C, Matlock D, Jenn C, et al. Establishing the effectiveness of patient decision aids: key constructs and measurement instruments. BMC Med Inform Decis Mak 2013;13(Suppl 2):S12. doi:10.1186/1472-6947-13-S2-S12
29. Hossler C, Levi BH, Simmons Z, Green MJ. Advance care planning for patients with ALS: feasibility of an interactive computer program. Amyotroph Lateral Scler 2011;12(3):172-7. doi: 10.3109/17482968.2010.509865
30. De Abreu MM, Gafni A, Ferraz MB. The use of a decision board to elicit Brazilian patients' and physicians' preferences for treatment: the case of lupus nephritis. Value Health 2011;14(5):S141-6. doi: 10.1016/j.jval.2011.05.015
31. Yazdany J, Feldman CH, Liu J, Ward MM, Fischer MA, Costenbader KH. Quality of care for incident lupus nephritis among Medicaid beneficiaries in the United States. Arthritis Care Res (Hoboken) 2014;66(4):617-24. doi: 10.1002/acr.22182
32. Hannemann-Weber H, Kessel M, Budych K, Schultz C. Shared communication processes within healthcare teams for rare diseases and their influence on healthcare professionals' innovative behavior and patient satisfaction. Implement Science 2011;6:40. doi: 10.1186/1748-5908-6-40
33. Budych K, Helms TM, Schultz C. How do patients with rare diseases experience the medical encounter? Exploring role behavior and its impact on patient-physician interaction. Health Policy 2012;105(2-3):154-64. doi: http://dx.doi.org/10.1016/j.healthpol.2012.02.018
34. Grut L, Kvam MH. Facing ignorance: people with rare disorders and their experiences with public health and welfare services. Scandinavian Journal of Disability Research 2012;15(1):20-32. doi:10.1080/15017419.2011.645870
35. Hughes RA, Sinha A, Higginson I, Down K, Leigh PN. Living with motor neurone disease: lives, experiences of services and suggestions for change. Health Soc Care Community 2005;13(1):64-74. doi: 10.1111/j.1365-2524.2005.00530.x
36. Gruis KL, Wren PA, Huggins JE. Amyotrophic lateral sclerosis patients' self-reported satisfaction with assistive technology. Muscle Nerve 2011;43(5):643-7. doi: 10.1002/mus.21951
37. Foley G, Timonen V, Hardiman O. Patients' perceptions of services and preferences for care in amyotrophic lateral sclerosis: a review. Amyotroph Lateral Scler 2012;13(1):11-24. doi: 10.3109/17482968.2011.607500
38. Foley G, Timonen V, Hardiman O. Acceptance and decision making in amyotrophic lateral sclerosis from a life-course perspective. Qual Health Res 2014;24(1):67-77. doi: 10.1177/1049732313516545

39. Charon R. Narrative medicine: a model for empathy, reflection, profession, and trust. JAMA 2001;286(15):1897-902. Available from: http://jama.jamanetwork.com/article.aspx?articleid=194300

40. Garrino L, Picco E, Finiguerra I, Rossi D, Simone P, Roccatello D. Living with and treating rare diseases: experiences of patients and professional health care providers. Qual Health Res 2015;25(5):636-51. doi: 10.1177/1049732315570116

41. Dwyer AA, Quinton R, Morin D, Pitteloud N. Identifying the unmet health needs of patients with congenital hypogonadotropic hypogonadism using a web-based needs assessment: implications for online interventions and peer-to-peer support. Orphanet J Rare Dis 2014;9:83. doi: 10.1186/1750-1172-9-83

ORIGINAL ARTICLE

Walking with McArdle disease: alienation and solidarity in a rare disease journey

Edmund Jessop
Specialised services team, NHS England, London, UK

Open access

Correspondence to
Edmund Jessop
Specialised services team
NHS England
80 London Road
SE1 6LH London - UK
Email edmund.jessop@nhs.net

Competing interests
None declared

Received: 30 October 2015
Accepted: 4 April 2016

The Rare Diseases and Orphan Drugs Journal has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under Grant Agreement n. 305690 RARE-Bestpractices project www.rarebestpractices.eu.
Sole responsibility lies with the authors and the European Commission is not responsible for any use that may be made of the information contained therein.

Abstract

Narrative reveals what the author wants to share with the reader. First-hand written narratives are a particularly valuable resource for understanding the lived experience (as opposed to the medical facts) of disease. Stacey Reason is a person with McArdle disease, a very rare disorder of muscle, who wrote an account of her 32-day trek across the countryside and mountains of Wales. Her narrative is in the form of a daily diary detailing the events of each day's walking, together with her thoughts and feelings. I present an inductive and semantic analysis of this text. Prominent themes include the alienation of having a rare disease, but also a strong sense of solidarity in the journey, and the normal pleasures and tribulations of walking the British countryside.

Key words

Friends, McArdle disease, narrative medicine, social alienation.

Introduction

As doctors, we focus on the processes of disease. We try to understand molecular mechanisms to guide our choice of drugs; we investigate disordered anatomy to offer corrective surgery; we investigate abnormal physiology. We know that the patient in front of us is a person, not a disease, but the practice of medicine requires us to tackle problems system by system, one by one. Attending to the hopes, fears and experiences of the whole person in front of us is difficult.

In this situation, the first hand testimony of patients is an invaluable resource for understanding the lived experience of an illness. For chronic illness, this testimony typically takes the form of narrative, an account of events unfolding over a period of time. The narrative may be spoken or written, but full length spoken narratives are rare. Also, analysis of spoken narrative is complicated by the need to observe tone and gesture as well as the words. Full length written narratives provide stable material with form, content and words carefully constructed by the author.

We often speak of patients' journeys, meaning a metaphorical journey from symptom to diagnosis, from one state of health to another, or from even life to death. In this paper I analyse the written narrative of a literal, physical journey – a trek made by four people with McArdle's disease. McArdle is an inherited disorder of muscle metabolism which affects about 1 person in 100,000. It limits the capacity for sustained muscle activity, including walking, but also everyday tasks such as opening a new jam jar.

The narrative seemed to me worthy of analysis because even on a casual reading two themes stood out strongly, and in contrast to my earlier analysis [1] of (metaphorical) patient journeys. Specifically there were strong themes of solidarity, in contrast to the loneliness evident in the accounts by rare disease patients of their journey to diagnosis; there was also a strong emphasis on named individuals in the telling of the journey, in contrast to the almost entirely nameless narratives I analysed in the previous paper [1].

Method

The material analysed here is text written by Stacey Reason in a book entitled 'One step at a time' [2]. The book is an account of a 32-day trek across Wales in the summer of 2010 by Reason and three others, all of whom have McArdle disease.

The book contains a considerable amount of other material, such as photographs and a daily blog, but I have chosen to focus on Reason's narrative. She writes a short introduction, followed by a page of 450-500 words for each of the 32 days of the journey, and an epilogue. Reason is a Canadian who writes in English.

The target audience for this narrative is stated on the book's cover to be 'patients, families and health professionals alike'. The author tells us that her purpose is as follows:

"… we wanted to share our experience with the world. We wanted to record our successes and challenges, what worked and what didn't. Most of all we wanted to demonstrate that people with McArdle disease can lead a normal, healthy productive life" *(day 9)*

My analytical method was inductive and semantic, following the 6 phase process outlined by Braun and Clarke [3]. An inductive process approaches the material with no preconceptions; a semantic analysis attends to the surface meaning of the narratives without seeking underlying hidden themes. First, I read the text several times to gain a thorough familiarity with the material. I then (phase 2) generated an initial list of ideas about the material. In phase 3, themes started to emerge, though in practice some themes emerged so strongly that this phase overlapped with phase 2 of Braun and Clarke's process. Ideas were grouped and sorted by grouping verbatim quotes, using standard word processing software. A particular text might appear under more than one theme. The themes were reviewed and refined (phase 4), and then (phase 5) named. Finally (phase 6) this report was written.

Results

Two clusters of themes stand out immediately from Reason's narrative, which we can name as alienation (feeling different from other people) and solidarity (being with other people).

Alienation

Reason opens her narrative thus:

"From early childhood you know there is something wrong. You try, but you cannot keep up with your friends… Every day, with everything you do, you fall behind… everyone. With no explanation at hand, you are left feeling embarrassed, humiliated, utterly defeated"

So from its very beginning, the narrative emphasizes the social consequence of the disease: embarrassment and humiliation. Note also however that this is attributed to the lack of diagnosis – "with no explanation at hand".

Anxiety is also prominent. At first it seems that the anxiety is a performance anxiety-fear of failure.

"…my old familiar preoccupations returned – anxiety, fear and panic" *(day 2)*

"I had been a little nervous about our first big mountain day, who am I kidding – I was petrified" *(day 3)*

"My first thought is uh oh! How will I ever manage to keep up?" *(day 13)*

"What I had to work on though, was the pervasive feelings of inadequacy" *(day 26)*

"Having lived thirty six years without a diagnosis, I was perpetually embarrassed with the ambiguity of my seemingly poor level of fitness" *(day 1)*

No suggestion is made in the narrative that the embarrassment and humiliation come from the comments or teasing of other people: these are internal states of mind. And the telling of the story demonstrates how these problems become less as the walk proceeds: at day 18 we read:

"I no longer was afraid or embarrassed" *(day 18)*

"Perhaps this was part of my journey, to not only accept my diagnosis of McArdle disease, but a more global affirmation of self" *(day 7)*

There are frequent references in the narrative to the sense of achievement, which is situated within the bounds of what is possible for people with McArdle disease:

"I had learned my limits, and now was not the time to aggressively challenge them" *(day 12)*

"…I can do anything I set my mind to. McArdle disease is, and always will be part of my life; but it is not my life" *(day 18)*

"We were walking for everyone else with McArdle's. Our struggles and our successes were theirs too... We wanted to reach out to more people, to empower them in the same way we had empowered one another" *(day 22)*

"So today I happily trod up and down the hills of Wales with my newfound developing courage and acceptance of this rare metabolic disease. I hope I can hang onto this feeling forever. Could you?" *(day 18)*

The phrase "Could you?" in the last quote addresses the reader directly, engaging him or her in the author's story. This is the only place in the narrative where this happens, so the reference to courage and acceptance is especially important.

Solidarity

The theme of alienation is matched by an equally strong theme of solidarity. It thus offers a counterpoint to the separation and alienation of rare disease.

Solidarity may consist in the immediate, physical presence of other people; or it may be the wider solidarity of our common experiences as ordinary people, human beings. Reason's narrative exhibits both types of solidarity.

Throughout the journey there are companions and helpers. In a previous analysis of rare disease narratives [1], I pointed out how rarely the actors were named. But in Reason's journey almost everyone she meets is identified by name. And in being named they are also honoured. For nowhere in this narrative do we find strangers who distance themselves from the McArdle walkers, none who taunt or tease.

"The group maintained contact with one another – forever connected" *(intro)*

"our kind hearted support driver" – this phrase appears in the second paragraph of the whole journey *(day 1)*

"Heather… fed us, cleaned up after us and nurtured us" *(day 8)*

"Meri shows us a different way of being in the world; of living in the moment, and being one with the world around her. I feel truly blessed to have met such a wonderful, creative, strong woman" *(day 15)*

"Dan, Andy and I were thoroughly enjoying the hospitality of the Wakelin siblings"

"The day culminated with a lovely dinner – all thirteen of us, together celebrating" *(day 26)*

Part of solidarity is to do what other people do – to be normal:

"We talked, we laughed, we ate – all pretty normal stuff" *(day 1)*

"…feeling normal is not familiar to us – so it felt great!" *(day 27)*

This solidarity of "feeling normal" and doing "pretty normal stuff" touches on our common experiences as ordinary people. Also normal, in travelogues from the British countryside, are accounts of getting lost, getting wet, and enjoying natural beauty. This conveys a sense of shared experience: enjoying the common feelings of trekking in the countryside – beauty, good weather, bad weather, getting lost and so on. So the narrative is full of the normal experiences, good and not so good, of walking in the countryside. The narrative is not wholly determined by illness.

Beauty is a prominent theme:

"The views… were breath-taking" *(day 11)*

"…the mountains and their magnificent proportions" *(day 6)*

"For now, I will enjoy the beauty that surrounds me…" *(day 8)*

"The west-east route… can only be described as breath-takingly majestic and gracefully alluring" *(day 19)*

So also is the weather:

"the weather was dismal… the rain fell heavy, and the wind carried it sideways – there was no escaping it" *(day 3)*

"The weather had turned for the worse – the winds were strong, the air was cold and I was certain it was snowing – okay, maybe they were just really cold raindrops" *(day 5)*

"the wet weather was relentless…" *(day 8)*

"The sun was shining and our mood was relaxed. It really was a perfect day" *(day 11)*

And getting lost:

"The map was telling us to go in one direction, the trail – another" *(day 14)*

"Lunch was followed by a second wrong turn" *(day 14)*

"But seriously, how many times can you get lost in the rain?" *(day 17)*

Discussion

Reason has provided first hand testimony of her experience over 32 days of walking in Wales. She comments on the daily events and reflects on present and past. Analysis of her narrative shows that themes of alienation and solidarity are prominent.

Alienation is the sense of being separate or different. Any illness makes us different from our fellow human beings, marks us out as alien. Sometimes this separation is temporary, as when a bout of sickness leaves us unable to share the family meal. But for genetic diseases, the separation is lifelong. It is from birth, and it may be profound:

"I thought I was the only one in the world, you see. In fact for a long time I used to comfort myself with the thought that actually I was an alien child. And I spent most of my childhood waiting for the mother ship to come back for me, to take me away" [4]

For common conditions such as diabetes and asthma, alienation may be overcome by finding fellow sufferers. But people with rare disorders typically know of no-one who shares their particular pattern of disability and dysfunction. For those with McArdle disease, which is primarily a limitation of motion, difference and alienation may be more obvious in the energetic days of youth than later on when a sedate pace is the norm. Spoiled identity [5] becomes obvious only when there is a requirement to keep up, to match the pace of people who do not have McArdle disease – as Reason comments "You try, but you cannot keep up with your friends". Even in adulthood, however, the sense of difference remains, with frequent reference in the narrative to fear of failure, embarrassment and anxiety.

Solidarity comes from the presence of fellow sufferers, people who share our particular same pattern of ability and disability, engagement and limitation. The comfort may be emotional, or it may be practical – tips and hints on how to manage particular actions and situations. In one sense, the whole journey narrated by Reason is a sharing of advice on how to manage a long distance walk across hill country. The walking group also clearly developed emotional solidarity – "forever connected" as Reason puts it.

The wider solidarity of common humanity can be illustrated by comparing Reason's narrative with two other accounts of long distance walks.

In the very same month as Reason was walking 338 kilometres across Wales, Simon Armitage, a professional poet, walked the 429 kilometres of the Pennine Way, a long distance footpath in England. Like Reason, Armitage also told the story of his journey a day at a time [6]. He mentions no specific locomotor disability, though he doubted his physical fitness: 'Physically, I'd assumed I wasn't up to it' (p 278). His text shows several points of solidarity with Reason in describing the common experiences of hillwalkers in Britain.

Armitage walked solo but an ever changing cast of companions accompanied him on various sections of the walk. Like Reason, he names them and celebrates them: "…my sincere thanks to the following, for their kindness and encouragement, for their time and energy, but mostly for their company…" (p 282). Armitage also shares with Reason the familiar anxieties of a hillwalker about getting lost in bad weather: "Fear is what is stopping me. I don't mind the wet and the cold, but I don't want to get lost" (pp 268-9).

In the telling of a narrative, the author selects what to include and what to leave out. A contrast to Reason and Armitage is provided by Ranulph Fiennes. Fiennes is a professional explorer whose book *Mind over Matter* [7] describes an attempt to walk unsupported across Antarctica. His companion in the 65-day journey was Mike Stroud, a doctor. Fiennes is an interesting character whose strengths and weaknesses have been revealed in his many books. His narrative is full of dry wit but is devoid of enjoyment; it is all about the struggle to survive and to keep moving. There is no mention of beauty in the ice fields. Although Stroud has saved Fiennes' life after a fall through the ice on a previous expedition (and in this journey Fiennes later does likewise for Stroud), there is little discussion of the emotional warmth that comes from companionship; references to his travelling companion by Fiennes focus almost entirely on whether Stroud will have the physical strength to complete the journey. Here is a typical passage:

"The next day, after two hours of steep yard-by-yard progress, Mike was forced by another diarrhoea attack to stop… A few minutes later he told me he could not continue. He must rest. I was furious. We erected the tent and made tea. After Mike had rested for an hour or two I told him we must get going. He was angry and said I was boorish and graceless; in short a prick of the first order" (p 139)

Antarctica is a harsh environment where life hangs by a thread; so perhaps the lack of enjoyment is dictated by the life-threatening dangers of the trek. But note that for people with McArdle's the same can be true of the north Wales hills: Reason's book is dedicated to a young woman, Jessica Binder, who died from McArdle's disease at the age of 31, and Reason herself was hospitalized on day 5 of her trek. Like Fiennes in Antarctica, Reason must make her walk step by step. So her frequent references to beauty and enjoyment, solidarity and kindness, rather than struggle and hardship, are worthy of note. Reason has an illness, but she is not defined by, or not fully defined by it: she still enjoys the normal experiences of common humanity.

MacIntyre [8] has drawn attention to our status as "dependent rational animals", all in our own way vulnerable and all in our own way dependent on help and support from our fellow human beings. Reason's narrative illustrates well this thesis.

References

1. Jessop E. The quest for diagnosis – a narrative analysis of patient journeys. Rare dis orphan drugs 2014;1:109-115.
2. Reason SL. One step at a time. Walking with McArdle disease. Droxford: Association for Glycogen Storage Disease (UK) 2013.
3. Braun V, Clarke V. Using thematic analysis in psychology. Qual Res Psychol 2006;3:77-101.
4. Cornwall S. Telling stories about intersex and Christianity: saying too much or not saying enough? Theology 2014;117(1):17-33.
5. Goffman E. Stigma: notes on the management of spoiled identity. Englewood Cliffs NJ: Prentice Hall 1963.
6. Armitage S. Walking home. London: Faber and Faber 2013.
7. Fiennes R. Mind over matter. London: Sinclair-Stevenson 1993.
8. MacIntyre A. Dependent rational animals. London: Duckworth 2009

Case Report

Familial case study: a recurrent metabolic disease in a Tunisian family

Nadia Ben Jamaa[1], Tanya Kitova[2], Moez Ben Amara[3], Denis Milkov[2], Dorra Zghal[4], Sami Jabnoun[3], Mohamed Yacoubi[5], Mahdi Khila[4], Imen Kessibi[3], Samia Kacem[3], Faouzia Zouari[4], Soumeya Siala-Gaigi[1], Aida Masmoudi[1]

[1]Department of Embryo-fetopathology, Center of Maternity and Neonatology of Tunis, Tunisia
[2]Medical University of Plovdiv, Bulgaria
[3]Department of Neonatology, Center of Maternity and Neonatology of Tunis, Tunisia
[4]Department of Gynecology and Obstetrics C, Center of Maternity and Neonatology of Tunis, Tunisia
[5]Department of Pathology, University Hospital Farhat Hached of Sousse, Tunisia

Open access

Correspondence to
Tanya Kitova
Department of Anatomy, Histology and Embryology
Medical University of Plovdiv
15A Vasil Aprilov Blvd
4002 Plovdiv, Bulgaria
Email: tanyakitova@yahoo.com

Competing interests
None declared

Received: 9 February 2015
Accepted: 2 April 2016

The Rare Diseases and Orphan Drugs Journal has received funding from the European Union Seventh Framework Programme (FP7/2007-2013) under Grant Agreement n. 305690 RARE-Bestpractices project www.rarebestpractices.eu.
Sole responsibility lies with the authors and the European Commission is not responsible for any use that may be made of the information contained therein.

Abstract

We report a recurrent case of Sly syndrome in a Tunisian family. The mother was a 32-year old, parity three, five gestations, from a first-degree consanguineous marriage. Her first pregnancy ended in a miscarriage; the second pregnancy ended with the birth of a healthy child. The other three pregnancies were interrupted through medical intervention due to hydrops fetalis.

The histological placental examination of the first two fetuses found cytoplasmic vacuolization affecting the trophoblast and Hofbauer cells (Hale coloration). The prenatal diagnosis by amniocentesis of the third pregnancy revealed a high level of glycosaminoglycans with a predominance of chondroitin sulfates in electrophoresis, confirming the diagnosis of Sly disease.

In conclusion, the histological examination of the placenta is essential for the biological and genetic examination, as a basis for the diagnosis of Sly disease and for a further genetic counseling.

Key words

Hofbauer cells, hydrops fetalis, mucopolysaccharidosis VII, placenta, Sly syndrome.

Introduction

Lysosomal storage diseases are a group of 50 inherited monogenic diseases that are characterized by malfunctioning lysosomes and an accumulation of unprocessed biopolymers in various tissues and organs. The clinical symptoms progressively develop with a coarsening of facial features, bone, skin, and eye changes, organomegaly and a severe retardation in the neuropsychological development. Lysosomal storage diseases belong to the group of rare diseases. As separate diseases, they are extremely rare, but the incidence of the group as a whole is 1 in 5000-7000. The most common classification of lysosomal storage diseases is according to the type of metabolite accumulating in lysosomes mucopolysaccharidoses, glycoproteinoses, sphingolipidoses and glycogenoses [1].

Mucopolysaccharidoses are a large heterogenous group caused by a deficit of any of the eleven enzymes involved in the metabolism of these biopolymers [2, 3]. They are characterized by an intracellular accumulation and increased excretion of mucopolysaccharides (glycosaminoglycans, GAGs) [2, 3]. Mucopolysaccharidosis type VII (MPS VII), or Sly syndrome, is a rare lysosomal storage disorder first described by Sly et al. in 1973 [4]. MPS VII occurs in less than 1 out of 250,000 births. It is an autosomal recessive disease caused by a deficiency of the enzyme β-glucuronidase, leading to a lysosomal accumulation of heparan, dermatan and chondroitin sulphate [5, 6]. The gene for β-glucuronidase is mapped to be at 7q 21.2-22.

According to the clinical symptoms, MPS can be divided into four phenotypes: MPS which predominantly affects the skeleton and soft tissues; MPS which only affects the skeleton and soft tissues; MPS which affects the skeleton; MPS which predominantly affects the central nervous system [8]. The diagnosis of lysosomal storage diseases and, in particular, of MPS VII is based on the histopathologic discovery of an accumulation of metabolites and a confirmation of an enzyme deficiency by electrophoresis.

The clinical diagnosis is always difficult due to the polymorphism of clinical symp-

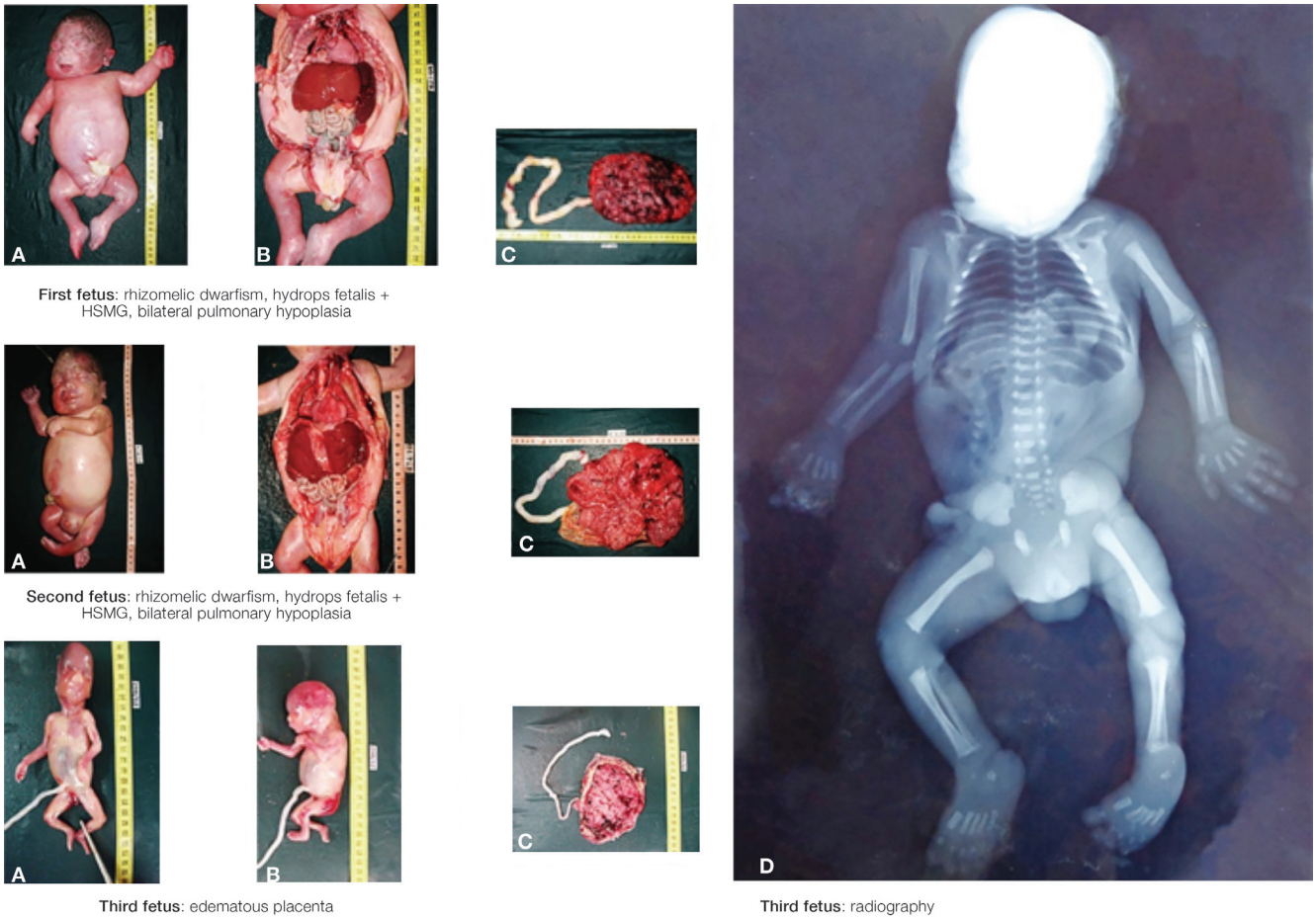

Figure 1. Macroscopic examination of the three fetuses and their placentas (left panel, A-C); radiography of the third fetus (right panel, D).

toms [7]. The genetic heterogeneity of lysosomal storage diseases limits the diagnostic and prognostic capabilities of a genomic analysis. The first ultrasound symptoms are always anasarca and a thickened nuchal fold in the first trimester, progressive ascites in the second trimester, and a pericephalical edema or a generalized edema of the body, often accompanied by ventriculomegaly. Facial dismorphia with an indentation of the middle level of the face was observed. There were also multiple hypertrophic epiphysal disostoses, fetal immobilization, vacuolated lymphocytes and anemia or thrombocytopenia.

Case presentation

We report a recurrent case of Sly syndrome in a Tunisian family and the treatment of this condition.

A 32-year old woman, parity three, five gestations, 0+ blood group from a first-degree consanguineous union. Her first pregnancy ended in a miscarriage; the second pregnancy ended with the birth of a healthy child (now a 6-year old daughter). The other three pregnancies were interrupted through medical intervention due to hydrops fetalis. The karyotypes of these three fetuses were normal. A fetal examination was performed in all three cases.

The three fetuses all had facial dismorphism – pericephalical edema in the first two fetuses and a thickened nuchal fold in the third fetus, hypertelorism and prominent infra-orbital folds, long philtrum, low-set and malformed ears (Figure 1A). All three fetuses had very short necks (Figure 1A).

In the three fetuses there were symptoms of multiple dysostosis, which in the first two fetuses was represented by a rhizomelic dwarfism (Figure 1A). The radiography of the third fetus shows multiple symptoms of dysostosis – shortened and thick proximal and distal ends of long bones, pes equinovarus and abnormalities of the vertebral bodies and arches. The epiphyses had a rugged contour (Figure 1D).

The three fetuses had hydrops, hepatosplenomegaly and bilateral pulmonary hypoplasia (Figure 1B). The brain examination found no neuropathological signs. The histological examination showed no abnormalities of the visceral organs in all autopsies. The macroscopic study found an edema of the placenta (Figure 1C). The microscopic

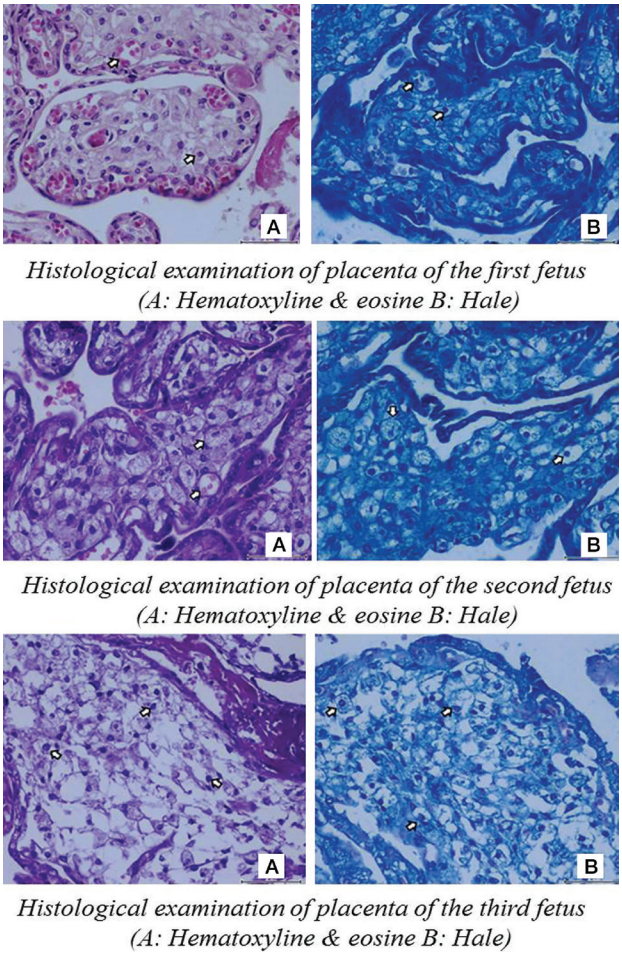

Figure 2. The histological examinations of the placentas.

examination of the placenta of the fetuses found evidence of accumulation-vacuolization of the Hofbauer cells.

The placenta of the second fetus had reproduced the same lesions and the Hale coloration showed cytoplasmic vacuolization affecting the trophoblast and Hofbauer cells-suggesting Sly syndrome (Figure 2).

The prenatal diagnosis by amniocentesis has been done for the third pregnancy. It revealed a high level of glycosaminoglycans with a predominance of chondroitin sulfates during the electrophoresis, confirming the diagnosis of Sly syndrome.

Conclusion

The association of hydrops fetalis, hepatosplenomegaly and multiple dysostosis with consanguinity is suggestive of a metabolic disease. The histological examination of the placenta is essential to diagnose Sly syndrome. The biological and genetic examinations confirm the diagnosis and may be used as a basis for counseling.

References

1. Maire I. Mucopolysaccharidose de type VII ou maladie de Sly. Encyclopédie Orphanet 1998.
2. Huynh HT, Grubb JH, Vogler C, Sly WS. Biochemical evidence for superior correction of neuronal storage by chemically modified enzyme in murine mucopolysaccharidosis VII. Proc Natl Acad Sci USA 2012;109(42):17022-7.
3. Rowan DJ, Tomatsu S, Grubb JH, Haupt B, Montaño AM, Oikawa H, Sosa AC, Chen A, Sly WS. Long circulating enzyme replacement therapy rescues bone pathology in mucopolysaccharidosis VII murine model. Mol Genet Metab 2012;107(1-2):161-72.
4. Rowan DJ, Tomatsu S, Grubb JH, Montaño AM, Sly WS. Assessment of bone dysplasia by micro-CT and glycosaminoglycan levels in mouse models for mucopolysaccharidosis type I, IIIA, IVA, and VII. J Inherit Metab Dis 2013;36(2):235-46.
5. Hytönen MK, Arumilli M, Lappalainen AK, Kallio H, Snellman M, Sainio K, Lohi H. A novel GUSB mutation in Brazilian terriers with severe skeletal abnormalities defines the disease as mucopolysaccharidosis VII. PLoS One 2012;7(7):e40281.
6. Huang YL, Li SY, Zhao XY, Fan LP, Lin WC, Zhou ZH, Cheng J, Liu L. Enzymatic diagnosis and clinical characteristics of 52 children with mucopolysaccharidosis. Zhongguo Dang Dai ErKeZaZhi 2012;14(7):510-4.
7. Beck M. Variable clinical presentation in lysosomal storage disease. J Inherit Metab Dis 2001;24(2);47-56.
8. Muenzer J. The mucopolysaccharidosis: a heterogeneouse group of disorders with variable pediatric presentation. J Pediatr 2004;144(5):S27-34.