ORIGINAL ARTICLE

A standard of care for the ultra-rare Marshall-Smith syndrome: developmental process and lessons learned

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Abstract
Within the framework of the Dutch Chronic Disease Management Program, standards of care are being developed for common and for rare diseases in The Netherlands. A standard of care describes the desired quality of care for a specific chronic disease from the patients' perspective. Here we describe a project in which we developed a standard of care for an ultra-rare disease, Marshall-Smith syndrome (MSS), between 2011 and 2014. There are only three patients known with MSS in The Netherlands and 45 in total worldwide. There is no written documentation about the care for individuals who are affected by MSS. Therefore professional caregivers are often faced with questions when advising treatments for specific symptoms of the disease. A standard of care provides information on possible symptom-specific treatments of MSS, optimal organisation of care and description of quality criteria for care from patient/parents perspective. Here we describe the methods used for patient consultation and the lessons learned from the development process. We provide a short summary of the main topics of the standard. English translation will be available for patients with MSS worldwide. For those aiming to develop quality care standards for ultra-rare disease(s), our approach might be useful to learn from or even to adopt.

Key words
International patient consultation, Marshall-Smith syndrome, standard of care, ultra-rare disease, patients' perspective.

Introduction

The Dutch chronic disease management program

At present, almost one third of the population in The Netherlands suffers from one or more chronic diseases [1]. Major factors contributing to this large proportion of chronically ill people are the aging of the population, lifestyle-diseases, increased survival due to better paediatric care, and increased recognition of mental disorders that often accompany a physical chronic illness [2]. As in most Western countries, chronic diseases are starting to impose an enormous financial and societal burden in the Netherlands. In order to deal more effectively with the problem of chronic diseases, in 2008 the Dutch government introduced the so-called Chronic Disease Management Program (CDMP). This is a proactive, multicomponent approach to healthcare delivery for people with a chronic disease [3].

The major components of the CDMP are:

- development and use of standards of care,
- enhanced cohesion between prevention and cure,
- self-management of the patient,
- more coherent and effectively functioning multidisciplinary health care teams

Standards of care

The first component to be realized is the development of a standard of care. A standard of care not only describes the desired quality of the care for a specific chronic disease from the patients' perspective [4], but also comprises the other three components of the CDMP as well. Shortly after the introduction of the CDMP, the development of

numerous standards of care was initiated. The very first standards dealt with various common chronic diseases, such as obesity [5], chronic obstructive pulmonary disease [6] and asthma [7]. Later on, rare diseases – almost always chronic in nature – received attention as well. In 2011 The Dutch Genetic Alliance (VSOP) started a project called "The Patient in the Centre" to develop 15 standards of care for various rare diseases [8]. This currently makes the VSOP one of the major standard of care developing institutes in the Netherlands.

As clinical guidelines are often lacking, these standards represent the major source of information for health care providers, making these standards even more important for people with rare diseases than for people suffering from other chronic diseases. Standards are formulated from the patients' perspective in cooperation with caregivers and preferably also with insurance companies [9]. The consultation of all involved parties ensures that the standard will be broadly supported during its implementation.

National coordination and uniform format

The development of standards of care is coordinated on a national level. At first, the so-called Coordination Platform Standards of Care was officially mandated to coordinate all Dutch parties developing standards of care. From 2013 onwards this task was allocated to the new National Health Care Institute[1], an independent administrative authority with, among others, the task of maintaining the level of quality, accessibility and affordability of health care in the Netherlands.

All national standards that are being developed should fit a uniform format that has a modular structure [4]. This comprises four chapters representing the four phases of the health continuum of any specific chronic disease: (1) Early recognition & prevention, (2) Diagnostics, (3) Treatment options and (4) Monitoring, relapse-prevention, revalidation and reintegration. For any specific chronic disease a standard describes disease-specific care, the quality indicators of this care, the organisational structure of the health care setting and different general care components. These components describe those aspects of care that are not disease-specific (e.g. self-management, preconception-care) [4].

Here we describe a project in which we developed a standard of care for the ultra-rare disease Marshall-Smith syndrome (MSS) [9]. Special emphasis was put on combining several methods of patient consultation in order to insure the effective incorporation of the patient perspective. In the document we describe a prerequisite step, which was needed to broaden our project's scope. Although originally written in Dutch[2], the English translation of the resulting document is expected to improve the care and quality of life for people with MSS all around the world. We believe that anyone who wants to develop standards of care or other types of quality standards for ultra-rare diseases can benefit from the approach described here.

Project description

Marshall-Smith syndrome and its community

The MSS is a genetic disease characterized by accelerated osseous maturation, failure to thrive, respiratory difficulties, facial dysmorphism and developmental delay [10, 11]. With less than 50 patients described in the literature worldwide, MSS is a very rare disease. Quite recently, the disease-causing gene has been identified [12]. Children with MSS can reach adulthood by improved management of symptoms [10]. In the Netherlands, three children are known to have MSS (Figure 1).

The syndrome is characterized by severe intellectual and multiple other disabilities. Malnutrition and respiratory infections are the most common sources of morbidity and are treated symptomatically. The syndrome is also associated with a range of organ-specific complications [10]. Almost all patients worldwide live at home with their families and need around-the-clock care. Everyday life of an individual with MSS, as well as that of his or her family, is greatly affected by this condition and the intensive care that it requires (Figure 2, left). Individuals with MSS often need specialized care in hospitals from a large number of different medical disciplines (Figure 2, right).

By the end of 2007, the first informative website about the syndrome had been launched by the Dutch Marshall Smith Research Foundation (MSSRF, www.marshallsmith.org). In a secured part of the website, families with children who were diagnosed with MSS could register and share information about their experiences of living with the condition. Since then, the Marshall-Smith community has evolved into a strong and active alliance helping professionals gather information for scientific research [13]. Today the community uses Facebook as its

Figure 1. Children with Marshall-Smith syndrome from The Netherlands (with permission from their parents).

[1]http://www.zorginstituutnederland.nl/

[2]The standard is available from: http://www.vsop.nl/zza/media/zorgstandaard/20141218-002/

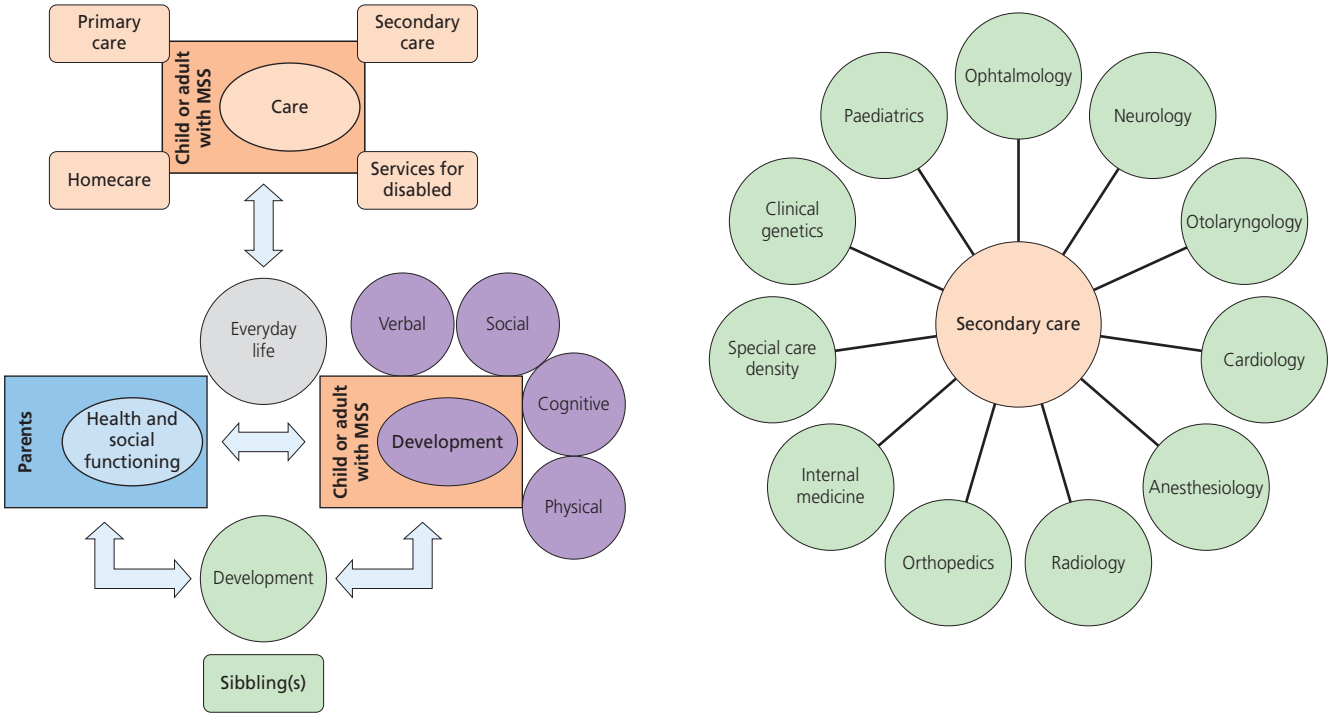

Figure 2. Left: complex interaction of care and everyday life in case of MSS. Right: disciplines involved in the highly specialized care of individuals with MSS.

main source of communication and counts 41 families who are affected by MSS from 17 countries (Figure 3). Without such a well-organized and active league, recruiting caregivers of MSS patients for our project would have been impossible.

Objectives and project organisation

The main objective of this project was to describe the optimal care that is needed for MSS patients based on reports of their parents and in close collaboration with professional caregivers. The resulting standard of care aims to provide professionals with guidance on how to deliver efficient and safe qualitative care for individuals with MSS and, if needed, for their families as well.

Figure 3. World map with location-signs of individuals with MSS based on registrations through the MSS website and Facebook-community: 41 individuals with MSS are shown in 17 countries.

The need for such a standard was evident. At the time of developing the standard of care there was no clinical guideline or best practice for treating MSS in the Netherlands. This was most probable due to the fact that there were only three patients in The Netherlands which were diagnosed with MSS and that happened when our project had just started. Professional caregivers are often faced with dilemmas on how to offer or advise a proper treatment. When confronted with possible new cases of MSS, professional caregivers have no written material to rely on for treatment options.

The project organisation was kept simple: for expert/medical-input and final approval of the standard, a think-tank was formed consisting of four experts from the Netherlands (a paediatrician, an occupational therapist, a paediatrician/clinical geneticist, and an adolescent psychiatrist) and one expert of clinical genetics from the United Kingdom. We also consulted a speech therapist, a child-anaesthesiologist, a rehabilitation specialist, a MD for the intellectually disabled, a dietician and an ENT specialist. After several rounds of consultation, including the presentation of the concept-standard of care to the three Dutch families, the final approval for the document was obtained from the complete think-tank and all the

members of the MSSRF board. The standard was written in Dutch by the current authors: a policy officer for rare diseases at the Dutch Genetic Alliance (VSOP) and the director of the MSSRF (also a parent of a child with MSS).

Challenges

When started, we were prepared for some well-known difficulties in patient-consultation when dealing with an ultra-rare disease. One of them is being the very limited number of patients with MSS in the Netherlands. To reach our objective of incorporating the patient perspective in a meaningful way, we planned an international patient consultation in English by an online questionnaire. Due to the scarcity of professional caregivers and experts on the syndrome, we directly turned to the professional caregivers of the three known patients in the Netherlands as well as to a known expert on MSS abroad.

However, during the course of the project, we were confronted with several additional problems. To that date there were less than 50 scientific publications available on the syndrome almost exclusively describing the phenotypic and/or genotypic aspects of MSS. There appeared to be little information – if any – about the full range of physical and mental symptoms, the many difficulties faced in everyday life, the handicaps, symptom-alleviating treatments and impact on the families. To resolve this problem, we broadened the scope of the project with a more detailed questionnaire for the parents of MSS patients to obtain knowledge of the unknown issues (e.g. about organ-specific symptoms, complications, treatments and about the cognitive and emotional problems their child is facing or has faced).

A further difficulty followed: such an elaborate and thorough questioning requires the use of the right medical terminology, which proved to be too difficult to comprehend for non-native English speaking parents. Some parents did not speak English at all. In the next section, we will describe the way we dealt with this obstacle.

Consultation methods

Originally we planned to consult parents of individuals with MSS by using an online questionnaire in English. The above mentioned obstacles required an adjustment of methodology and planning. By including more languages, combining different methods and media we aimed to resolve the hurdles we were faced with and to reach as many parents as possible for their input (Table 1).

The questionnaire was developed in Dutch in cooperation with Dutch parents of children with MSS and by the think-tank. The online questionnaire (in Dutch and English) contained in total 407 questions about:

- general information about the caregiver filling in the questionnaire and about the person with MSS,
- the care, information and needs in the first period after birth of the child with MSS,
- the process of getting the correct diagnosis and the satisfaction with this process,
- the current organisation of care (e.g. having a care-plan or case-manager),
- function-specific (e.g. breathing), or organ-specific (e.g. eyes)-symptoms/complications and their treatment(s)/use of an aid as well as the effect of and experience with treatment(s)/aid,
- cognitive, emotional and behavioural symptoms/complications and their treatment as well as the effect of and experience with the treatment(s),
- measures that have been taken by professional caregivers to prevent the different physical, cognitive/mental/behavioural complication or deterioration,
- nursing and homecare (living situation, professional caregivers),
- how the syndrome affected the family members.

Not all questions were obligatory: the online survey software made it possible to skip questions that were not applicable for the individual with MSS in question. Every topic-section (see bulleted list above) contained a single or multiple-choice answer-possibility and at least

Table 1. Methods, media and languages used to consult parents of individuals with MSS

Methods and media used	Direct purpose
Face-to-face interviews at homes, during the MSS family-days and through Skype	Gathering additional topics to those published in the MSS literature in order to develop a questionnaire for parents
Online questionnaire in Dutch	Reaching all parents in The Netherlands
Online questionnaire in English (translated from the original Dutch questionnaire)	Reaching native or well-speaking non-native parents
E-mailed questionnaire in Croatian (translated from the original Dutch questionnaire)	Reaching parents in Croatia
Taking the questionnaire by telephone in Spanish, German and French by a sworn interpreter	Getting feedback from parents living in Mexico, Germany and France and not (sufficiently) speaking English to fill in the online English questionnaire.

one open-ended-question. The time required to fill in the questionnaire was approximately one hour.

Summary of outcomes

Seventeen parents in total answered the questionnaire in one of the five languages (the age of individuals with MSS ranged from 1 to 27 years). With ten of the parents who answered our questionnaire we held a prior face-to-face interview (Table 1). The answers were transferred into an Excel worksheet. The closed-ended questions were summarized in tables. Open-ended questions were sorted separately by topic and question ID.

Our thorough approach of patient consultation yielded the information that was needed for the development of the standard of care. Some reoccurring entries that were described:

- unknown physical and mental symptoms and handicaps and the ways these were treated or dealt with;
- the effects of these treatments from parental perspective;
- the gaps and bottlenecks in care and their solutions from parental perspective;
- details of everyday life and the psychosocial impact on parents and siblings;
- a more comprehensive picture of the syndrome's natural history.

In the final standard of care we reference the results gathered by the patient-consultation 65 times.

A description of the content of the standard of care is beyond the scope of this article. We will however mention a few major features that are specific for this standard of care here (in contrast to most of the standards on rare disease and in contrast to the uniform format):

- care for MSS is divided into an acute phase and chronic phase. By doing this, we were able to describe the signs and symptoms, complications and their treatments in each phase, making the standard easier to use by caregivers;
- description of the burden disease for the individual with MSS and parents follows the above mentioned phasic division;
- a subchapter is devoted to palliation and possible early death;
- the chapter about the organisation of the care follows again the division in acute and chronic phase. This made it possible to pinpoint phase-specific bottlenecks in the organisation of care and give solutions to these from patients' perspective. Especially, the chronic, lifelong phase is described in detail including specific tasks and responsibilities of all stakeholders (parents, case-manager, professional caregivers and scientific expert). The major problem of health care organisation/ continuity of care during the transition between children to adult's life is addressed in detail: the transition period in the hospital should be gradual, including transferal of knowledge and tasks of the paediatrician to the new responsible clinician, the MD for the intellectually disabled. All stakeholders should be involved in this process: the young adult with MSS, his/her parents, the case-manager, the paediatrician and the MD for the intellectually disabled. Depending on the needs, abilities and level of development of the person with MSS, this process will start and end at different ages for each individual with MSS.

Practical coordination between specialists is the task of the case-manager in dialogue with the parents;

- we refer to as much as 20 national and international symptom-specific guidelines that should be followed during treatments;
- we refer to 17 other quality documents concerning different symptom-specific domains and health-care segments in The Netherlands;
- the standard contains referrals to 5 general care-components[3] regarding treatment of rare diseases [14-18] and 2 general care-components[4] regarding chronic diseases in general [19, 20].

To our knowledge, no other project has tried to develop a (national) standard of care by undertaking an international consultation of patients and their caregivers.

A main shortcoming of the current project was that it was not aimed at developing an internationally usable (English version) standard of care from the start. Though the Dutch ministry of health has made major steps in improving its policy regarding rare diseases in the Netherlands [21], in the current funding, nationally oriented and in Dutch written standard was one of the major criteria for granting.

Lessons learned and plans for the future

Patients' perspective is the anchor of standards of care. Information mirroring patients' experiences, satisfaction, needs and expectations has to be robust and representative for the affected population. In case of common chronic diseases this can be achieved through well-designed surveys and quantitative data analysis. In case of (ultra-)rare diseases, however, this represents a challenge because of the lack of patients. By gathering data internationally, one can try and overcome this hurdle.

In the course of our project, we found that besides a sufficient number of ultra-rare disease patients to recruit, the methods that can be used to gather patients' feedback

[3]Regarding communication and education, pharmaceutical care, heredity, psychosocial care and registries for rare diseases.

[4]Regarding nutrition and palliation.

also presented a bottleneck. Contrary to the relatively "common" and therefore well-described rare diseases like neurofibromatosis type 1 or Noonan syndrome, in which cases patients can be consulted through (online) questionnaires, this turned out not to work well enough in the case of this ultra-rare disease. Ultra rare diseases are often complex syndromes [13] with a yet to be described full range of symptoms and possible treatments. To overcome these problems, the use of questionnaires to assess these issues was supplemented by other methods of patient consultation (Table 1).

More recently, a follow-up project has been funded[5] during which several steps will be undertaken to make the standard accepted and usable worldwide. The first step will be to reformulate the current document into a more patient friendly document. This will be done in Dutch. This will then be earmarked as the Dutch patient-version of the standard aimed at parents of the Dutch children with MSS. The organisational chapter of the standard will have two versions: one for the above mentioned Dutch patient-version and another one that will be part of the English patient version of the standard[6]. Next, the Dutch patient-version of the standard including the internationally oriented organisational chapter will be translated into English and made available for English speaking parents of children and adults with MSS worldwide. With such a standard at their fingertips, parents will be able to approach their caregivers in order to get the optimal and up-to-date treatment for their children worldwide.

Together with the scientific experts, the MSSRF aims to set up a worldwide patient registry. Such a registry would help keep the standard up-to-date by having the data at hand to revise the document when needed. If this plan works, there would be no theoretical obstacle any more to provide optimal care and developmental possibilities for individuals with this severe handicapping condition.

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[5]Starting by March 2015 in cooperation between VSOP and the MSSRF.

[6]The organizational chapter in the English version will not contain information concerning the Dutch health care system, but will focus on more general information, like the tasks of a case-manager, the minimal information needed in the care-plan, information parents need in the different phases of the care, etc.

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