Genetics in Medicine Open (2023) 1, 100825

Genetics in Medicine OPEN
An Official Journal of the ACMG
www.journals.elsevier.com/genetics-in-medicine-open

REVIEW

The diagnosis communication process in spinal muscular atrophy: A cross-cutting view of the new challenges facing the therapeutic era

Eulàlia Rovira-Moreno[1,2], Anna Abulí[1,2], Patricia Muñoz-Cabello[1,2], Marta Codina-Solà[1,2], Eva Baillès[3], Mencía de Lemus[4], Basil T. Darras[5], Eduardo F. Tizzano[1,2,*]

[1]Department of Clinical and Molecular Genetics and Medicine Genetics Group, VHIR, University Hospital Vall d'Hebron, Barcelona, Spain; [2]Member of the European Reference Network on Rare Congenital Malformations and Rare Intellectual Disability ERN-ITHACA [EU Framework Partnership Agreement ID: 3HP-HP-FPA ERN-01-2016/739516]; [3]Department of Psychiatry, University Hospital Vall d'Hebron, Barcelona, Spain; [4]Patient Representative, Head of FundAME, Spain & Delegate of SMA Europe e. V., Freiburg, Germany; [5]Department of Neurology, Neuromuscular Program, Boston Children's Hospital, Harvard Medical School, Boston, MA

ARTICLE INFO

Article history:
Received 13 December 2022
Received in revised form
26 June 2023
Accepted 29 June 2023
Available online 5 July 2023

Keywords:
Communication of diagnosis
Genetic counseling
Psychological impact
Spinal muscular atrophy
Treatment decision making

ABSTRACT

Spinal muscular atrophy (SMA) is a prevalent severe genetic condition that follows an autosomal recessive inheritance pattern. Over the last decade, advances in innovative therapies have improved the course of the disease for many patients. There is evidence that early diagnosis and therapeutic intervention contribute toward better outcomes for these patients. The implementation of SMA newborn screening allows presymptomatic diagnosis leading to new communication scenarios, which poses opportunities and challenges when discussing possible treatment and evolution with families. Communication skills are essential to transmit accurate and comprehensive information to promote better coping and facilitate shared treatment decisions considering patient, family, and physicians' points of view. The role of professionals is increasing as patients live longer and present evolving phenotypes. Therefore, multidisciplinary follow-up has emerged as an essential component of the standard of care protocol for patients with SMA. On the other hand, issues regarding communication of the diagnosis to a new patient still deserve a thorough discussion to better accommodate the complexity of the different situations. We present this review as a cross-cutting perspective involving health care practitioners, genetic counselors, psychologists, and caregivers to further elaborate and guide the communication process of an SMA diagnosis under several settings.

The Article Publishing Charge (APC) for this article was paid by Medicine Genetics Group, VHIR.

*Correspondence and requests for materials should be addressed to Eduardo F. Tizzano, Department of Clinical and Molecular Genetics, Hospital Vall d'Hebron, 08035 Barcelona, Spain. *Email address:* eduardo.tizzano@vallhebron.cat

doi: https://doi.org/10.1016/j.gimo.2023.100825

The current therapeutic context in spinal muscular atrophy

Spinal muscular atrophy (SMA), an autosomal recessive disorder linked to 5q, is caused by pathogenic variants in the *SMN1* gene. SMA is a neuromuscular disorder characterized by progressive degeneration and loss of alpha motor neurons located in anterior horn cells of the spinal cord. It is one of the most prevalent, severe hereditary disorders of babyhood and early childhood; its estimated incidence is around 1 of 6000 to 1 of 10,000 live births, with a heterozygous carrier frequency of between 1 of 35 and 1 of 50.[1]

SMA is considered to encompass a range of clinical presentations of muscle weakness ranging from a severe congenital phenotype to minimal manifestations in adulthood. To better define functional performances, SMA has been classified into 3 basic types according to age at onset and maximum milestones reached. In type I, the severest, patients never sit unsupported and, according to natural history studies, before the discovery of new treatments, over 90% of these patients would have died by the age of 2.[2,3] In type II, an intermediate form, patients can sit but not walk independently and are wheelchair dependent. They face important comorbidities and a lack of autonomy that greatly affect their quality of life. In type III, patients are able to walk independently at some stage but usually lose this ability. Apart from these 3 main types, there is type 0—a congenital form—and type IV—an adult form—completing the SMA spectrum. Independent of the SMA type, the disease is caused by insufficient quantities of the protein SMN that is encoded by the genes Survival motor neuron 1 (*SMN1*) and Survival motor neuron 2 (*SMN2*).[4,5] *SMN1* is absent or mutated in patients with SMA, whereas *SMN2* is always present at a varying copy number (from 1 to 5). The *SMN2*-derived SMN protein is mostly truncated (delta7); however, even low amounts of a full-length form can maintain the patient alive though presenting varying degrees of severity, which is inversely dependent on the number of *SMN2* genes present (the more, the better).[6,7]

Specific relevant advances occurred in SMA during the last few decades. The *SMN1* gene was defined as determinant in the disease[8] and the modifier role of *SMN2* was clarified; the development of animal models helped establish preclinical studies for testing specific alternative therapies. Subsequently, human clinical trials were initiated, and currently, 3 advanced SMN-dependent SMA therapies are already approved by the Food and Drug Administration and European Medicines Agency: an antisense oligonucleotide affecting the splicing of pre-mRNA (nusinersen-Spinraza),[9] gene therapy with a self-complementary adeno-associated virus serotype 9 (Onasemnogene Abeparvovec, ZolgenSMA),[10] and an oral splicing modifier compound (risdiplam - Evrysdi).[11] Different clinical trials have demonstrated their effectiveness as transformative therapies, changing trajectories and phenotypes.[12]

Historically, SMA has been related to a recognizable clinical diagnosis, most cases being suspected when faced with severe early-presentation forms in comparison with chronic types that have a less typical clinical picture. Confirmation of the diagnosis is essential in both scenarios because timely diagnosis is crucial to avoid with early treatment the rapid motor neuron death in severe cases, and it ends the diagnosis odyseey allowing consider therapy in late-onset cases. Balancing the situation, once suspected, the genetics of this disease is very straightforward and these challenges can be resolved in 95% of cases with an uncomplicated genetic test, regardless of the phenotype. The arrival of the therapeutic era led to the initiation of prevention and proactivity to confirm SMA as soon as possible, with a current perspective to implement newborn screening in different countries.[13-15]

The scientific advances and therapeutic approvals have been so fast, that when facing a newly diagnosed patient, several issues regarding communication of the disease to the patient and their family still deserve a thorough discussion to better accommodate the complexity of the different situations. We present this review as a cross-cutting perspective involving health care practitioners, genetic counselors, psychologists, and caregivers to further elaborate and guide the communication process of an SMA diagnosis under several settings.

Main aspects facing a new SMA diagnosis based on prevention scenarios

One of the main duties of health care practitioners is to transmit adequate and complete information to patients and families in order to make the best decisions regarding their medical care. Health care resource allocations, on the other hand, are often made by government agencies with specific indications and limitations. In some countries, access to therapeutic options is limited by their cost and this obviously also has impacts on the parent's decisions and management of their expectations. Thus, it is relevant to establish good communication for all families, facilitating an informed decision concerning available therapeutic options and the adequate management of expectations regarding the efficacy of treatments. Indeed, by limiting access to medications in specific patient groups, the system pretends to balance the impact of the burden of such costs on health systems and society, though the principles of justice and equity may be distorted in some situations.[16]

The communication of an SMA diagnosis can occur in diverse scenarios, which correspond to different prevention levels, and the impact of the results may differ in each situation. Figure 1 summarizes the possible communication scenarios while informing the SMA diagnosis together with the levels of prevention.

Tertiary prevention: Corresponds to symptomatic diagnosis, treating patients who manifest the disease. The main influence of tertiary prevention is observed in standard of care and the appearance of evolving phenotypes. The communication of the diagnosis in symptomatic patients

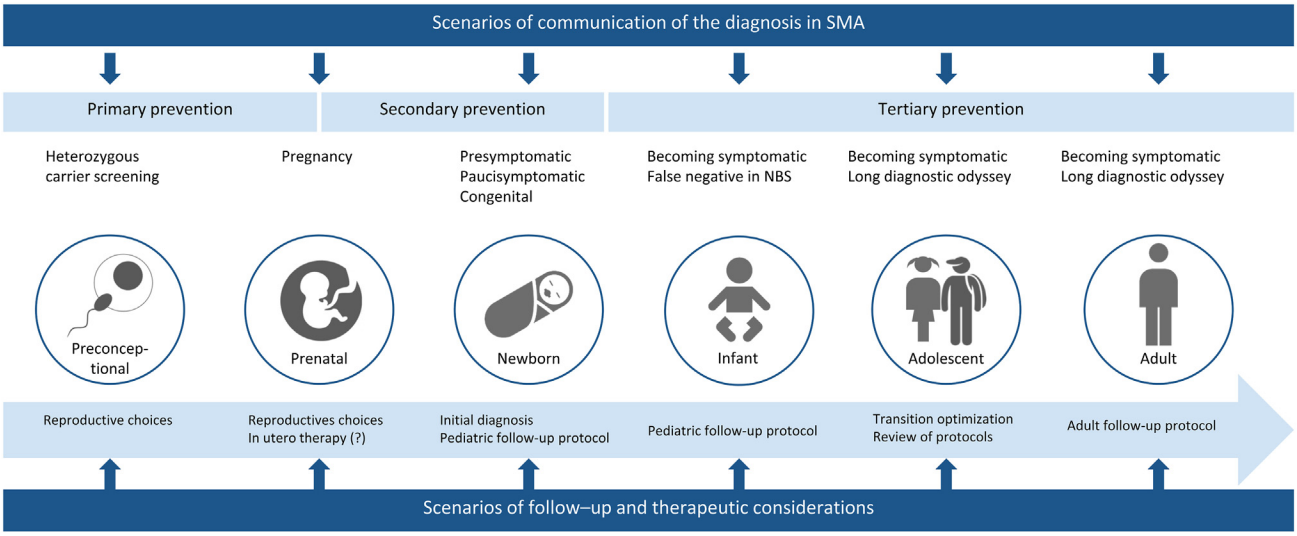

Figure 1 Present and future scenarios of communication of the diagnosis in SMA, follow-up, and therapeutic considerations. The possible communication scenarios are classified regarding the different levels of prevention. Preconception screening and prenatal testing allow decision making regarding reproductive options. At birth, because of newborn screening, most cases are expected to be presymptomatic or paucisymptomatic. In infancy, we should contemplate babies that become symptomatic either because there was no newborn screening or they were not detected via newborn screening (ie, a false negative with point pathogenic variants). Adolescence is marked by becoming symptomatic or confirmation of the diagnosis after a long diagnostic odyssey. Transition optimization should be implemented in already-known cases. In adults, manifestations may appear or be the result of a final diagnosis after a long odyssey for the patient. SMA, spinal muscular atrophy; NBS, newborn screening.

poses challenges, such as offering information regarding the prognosis, considering not only *SMN2* copy number and clinical variability but also the impact of treatment availability. Before the development of specific therapies, prognosis relied on the age at which symptoms appeared and the patient's maximum motor function. The *SMN2* copy number would also act as a disease severity predictor. Thus, later onset and harboring more *SMN2* copies correlated with better disease evolution. However, variability remains between patients and the *SMN2* copy number—disease severity correlation is not perfect and is sometimes erroneously ascribed.[7]

Secondary prevention: Aims to diagnose the patient before the disease is fully developed or manifested and can be postnatal (for example, via newborn screening) or prenatal (previous SMA history or prenatal screening). The main influence of treatment in the scenario of secondary prevention is reflected in the burden and development of disease. Newborn screening programs are being implemented worldwide; however, a small percentage of cases, those with infrequent pathogenic variants, will be not detected given that screening only detects cases where the *SMN1* gene is deleted biallelically. The communication of the diagnosis in presymptomatic patients, such as those diagnosed via newborn or prenatal screening, results in an earlier genetic diagnosis without any clear clinical manifestations or even without. Therefore, excluding those with a previous case in the family, parents usually have no information about SMA and were not aware of the possibility of their child having this disease. In these patients, the age of onset is unknown and the only available prognostic factor is the number of *SMN2* copies, which, in symptomatic cases, may also be inaccurate. Patients harboring 4 *SMN2* copies are particularly controversial to initiate treatment immediately, given that most patients will not develop symptoms during infancy.[17,18] An in-depth study of the *SMN2* genes and the validation of other biomarkers are eagerly awaited for use in clinical practice as prognostic factors to solve these situations.[17]

Primary prevention: Aims to detect SMA heterozygotes via population screening (preconception).[19,20] The objective is to offer genetic counseling to those couples with an increased risk. Facilitating information about their heterozygous carrier status empowers couples, allowing them to make informed decisions regarding their reproductive future. These actions may influence the incidence and/or prevalence of the disease.[21]

Communication of the diagnosis. Who gives the diagnosis?

SMA is usually suspected by pediatricians and child neurologists. The implementation of newborn screening in several countries and regions around the world is currently detecting genetically confirmed patients with SMA. Thus, instead of an alert floppy baby with breathing difficulties (Type I), an infant who is not standing/walking independently (type II), or a child having frequent falls and an atypical gait (type III), we are starting to see patients with a genetic diagnosis but without any specific manifestations or with prodromic isolated findings as a pauci-symptomatic picture.[12,13,22,23] Communication skills are essential to provide the patient or the family with

accurate information to accomplish an effective and comprehensive way to inform them about the characteristics of the disease. It is important, at this stage, to adequately assess both the understanding of the information being shared with the patient and caregivers and the need for psychological support.[24-27] In this context, genetic counselors are prepared to communicate bad news, whereas health care providers have the necessary knowledge regarding the trajectories and complications of the disease. Preferably, both aspects should be considered when facing the communication of a new SMA diagnosis. Information about standard of care, therapeutic options, and the adequate support required by the families should also be provided. Health care professionals have to deal with several situations that pose a challenge when passing on complex information, as in the case of SMA. Therefore, patients should be given the option of referral to health care professionals with in-depth knowledge of the disease and the currently available therapeutic options; this is important because SMA is a rare disease whose therapies are evolving very quickly and not all health care practitioners or geneticists are up to date[28] with all the recent advances in the field. In addition, gradual information can allow parents to readjust and handle the new situation better. Thus, adequate information before and after genetic testing facilitates the assimilation of the diagnosis.[29] Facing a new diagnosis poses challenges to both specialists and families. The process implies several steps and issues beyond the communication itself, such as the facilitation of details regarding the disease and its personal and familial implications, the correct understanding of the information received, which is crucial for the shared decision-making process to weigh up treatment options and adherence to an integral follow-up. The biopsychosocial model considers not only biological aspects but also psychological and social elements, reinforcing the relevance of a multidisciplinary team (see Figure 2 for further explanation).

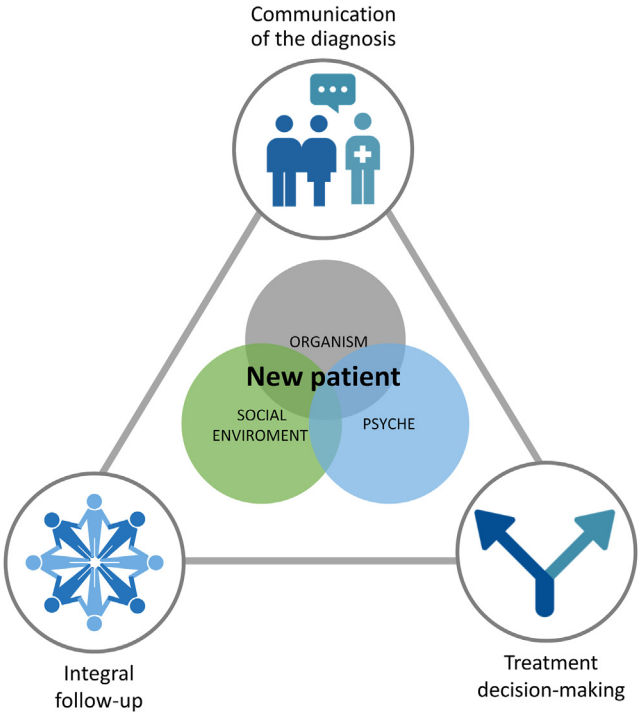

Figure 2 Facing a new patient with SMA. The center of the triangle represents the biopsychosocial model, which considers the 3 main aspects of an individual: the organism itself, psyche, and social environment. The organism refers to biological elements such as age, gender, phenotype or genetics; the psyche refers to mental and emotional health, beliefs, and expectations. Social environment refers to relationships, social support, and socioeconomic elements. The three factors of the biopsychosocial model should be considered during the diagnostic process, which includes communication of the diagnosis, integral follow-up, and treatment decision making. Further explanation in the text. Based on Tizzano et al, Serra-Juhe et al, and Gliedt et al.[12,21,30]

Coping with bad news in the family. Who receives the diagnosis?

The emotional emergency: Coping with the diagnosis

The adequate communication of an SMA diagnosis is challenging in several aspects, such as the complexity of the genetic mechanism, the wide range of clinical manifestations and the psychosocial implications (Figures 2 and 3). Parenting an infant with a rare disease has an impact on various aspects such as family dynamics, relatives' emotional state, and financial distress.[25] Unmet needs in rare diseases include the lack of psychological and social support.[26] Families with an SMA diagnosis state that there is usually little awareness of the disease in the general population, which may lead them to experience disbelief or socially unrecognized grief.[31] Furthermore, the lack of emotional support from health care professionals triggers negative experiences. Parents whose emotions were addressed during the appointment stated more positive experiences.[32]

The initial experiences of the parents with health professionals produce a great impact on their coping with the diagnosis. Different coping approaches have been defined, including problem- and emotion-focused coping.[24] The former involves the management of the situation by obtaining information, taking part in actions and decisions, or investigating alternative therapies. Emotion-focused coping involves the emotional response to the problem, such as retaining hope, seeking social support, and focusing on the child's possibilities for a good outcome rather than their disabilities. Both strategies have been observed in the coping process of parents who have a newborn child with a severe disability and a life-threatening disease.[27]

The perception of stressful events is very much influenced by personality, which is considered essential to cope with an unexpected bad situation.[33] An association between personality and coping styles had been described previously, with the neurotic trait having a positive correlation with

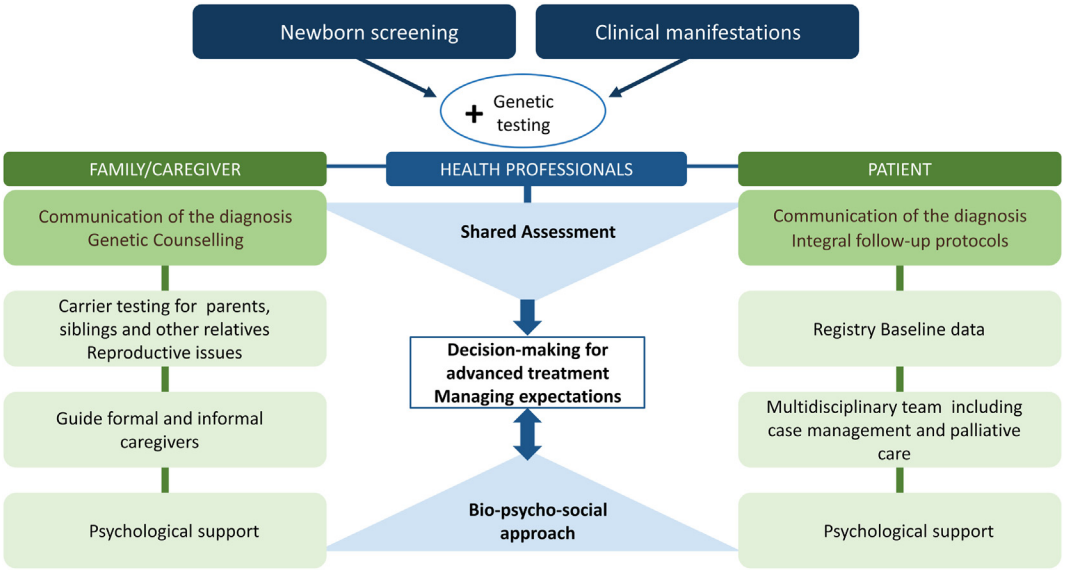

Figure 3 The processes to be covered by health professionals facing a new SMA patient. New patients may be detected by genetic confirmation via newborn screening or because of clinical manifestations. Adequate communication of the diagnosis to the patient should be performed according to age or family caregivers. Genetic counseling and integral follow-up protocols should also be provided. In the end, the process merges into a shared assessment of treatment decision making and managing expectations, always considering the bio-psycho-social integral approach (see Figure 2 for further explanation). Psychological support is always required.

avoidant coping policies and a negative correlation with a task-oriented approach.[33] Personality and coping strategies influence physical health.[34] Indeed, personality traits have a cardinal role with regard to the intensity of the emotional distress generated when facing the consequences and difficulties arising during the evolution of the disease (Figure 4).

Most parents recall the diagnostic experience as negative and felt that they could not take an active part during the medical appointment. Usually, parents found that knowledge was not empowering and felt frustration and helplessness at the moment of diagnosis. It is relevant to facilitate accurate information during the communication of

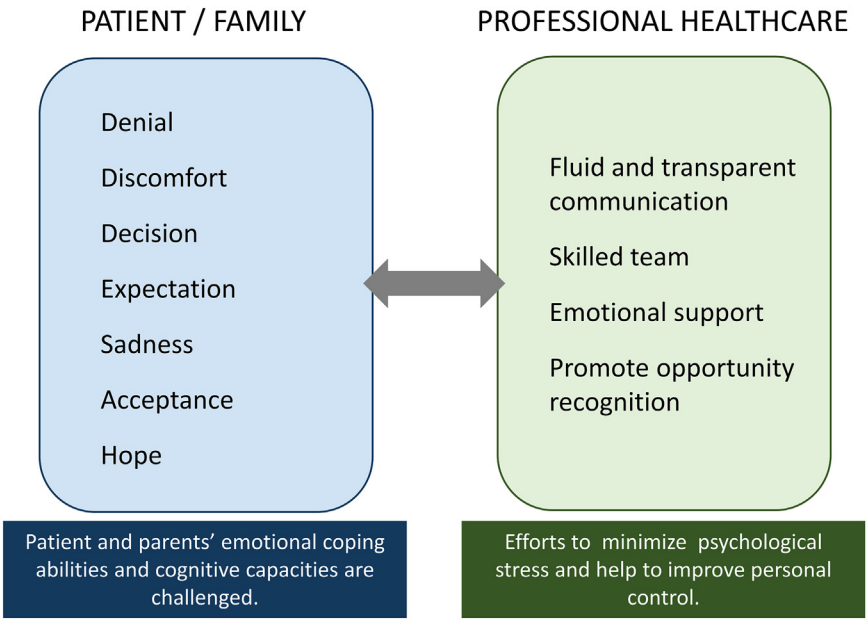

Figure 4 Issues and concerns arising when communicating the SMA diagnosis. The left section compiles possible adaptive reactions and attitudes of the patient and their family, organized according to the different stages of grief, which usually starts as denial and ends as hope. However, depending on the personality of the patients/families, coping styles and strategies may vary for each case, with different adaptive reactions (ie, starting with acceptance). To help patients/families face and resolve the different stages of grief, the health care professionals responsible for the communication process may consider the alternative approaches outlined in the right-hand section.

the diagnosis avoiding technical language because parents find it difficult to assimilate. Frequently, parents do not retain all the information given because the emotional impact may affect their ability to process it[29] (adaptive reactions and attitudes are listed in Figure 4). Negative experiences were strongly related to a lack of emotional support and denial of the disease is usually the first reaction.[35] This becomes especially pertinent in the neonatal screening context. Usually, there is null awareness during pregnancy about this procedure and, in the immediate postnatal scenario, the information about the disease being screened is rather limited. Parents go home with a healthy baby and a few weeks later they receive a call that implies that something is not going well. The situation is compounded by a cascade of doubts, anxiety, and expectations that are not helpful to guarantee an adequate communication process and decision making regarding possible therapies or palliative care. Moreover, parents only have an extremely short period of time available to make therapeutic decisions when a neonate with SMA is genetically confirmed (see *Promoting family involvement in shared treatment decision-making* section).

The main relevant aspects faced by parents in SMA diagnosis include the impact on the parent's emotional response, the necessity to do something for their child, and the challenge of dealing with uncertainty.[27] Families receiving a new genetic diagnosis are in a state of emotional emergency and are confronted with a huge amount of information, which also generates many questions that remain unanswered. Psychological support is necessary to switch from the traditional management of grief to the actual scenario promoting hope and opportunity (Figure 4).

Emotional distress decreased when parents could take action, which is easier with a confirmed diagnosis. In this sense, the availability of therapeutic options for SMA may facilitate the coping process, reducing the parent's emotional distress. Interestingly, when informing a diagnosis, fewer negative experiences were observed in parents who had undergone a longer diagnostic odyssey because they might be more prepared to receive the definitive confirmation[27] (Figure 1). Certainly, parents noticing their child as severely ill reported more accommodative strategies when receiving the diagnosis.[29]

Next step: Disclosure of familial communication

Genetic information does not only involve the patient but also their family members.[36] Therefore, when an individual receives a diagnosis, it does not only affect that person but also their relatives because they may be at risk of being heterozygotes or developing the disease. First-degree relatives are more frequently informed by the patient or their parents than by other relatives; health care providers should highlight the joint responsibility for communicating the conveyed information to other relatives, addressing factors such as consequences of disclosure or non-disclosure, what to disclose, timing of the disclosure, and communication strategies, which may include a letter to facilitate the familial disclosure of relevant information.[36] In SMA, familial communication allows relatives to be aware of the risk of being heterozygote, as well as to receive reproductive genetic counseling. Communicating the diagnosis to the family is not characterized as a single event but rather as an ongoing process. The disclosure of genetic information with relatives is complex, including communication with the patient's siblings.[20,31]

Usually, minors are less likely to be told about any genetic disease occurring within their family.[36] In the case of the siblings of patients with SMA, they may also be at risk, not only of being heterozygotes but also of developing the disease depending on the patient's characteristics. Not communicating this information to siblings may lead to misconceptions producing a negative impact on them. For example, some patients may deduce they can develop the disease when they are not at risk. The implementation of screening programs (ie, preconception or newborn) may increase the possibility of presymptomatic genetic testing in underage patients.[20,21]

Promoting family involvement in shared treatment decision making

The emergence of therapies poses opportunities and challenges when discussing possible treatment with the patient and their family.[37] Once the communication process is initiated, the emergency situation impacts the patient and their parents, particularly in the neonatal and infancy context. In the coping process of bad news, the main issues that have been identified include the construction of future images, perceptions of the child's limits and potentials, communication with health care professionals, expectations from the health care system, and the identification of possible actions, such as empowerment, proactive follow-up, and therapies.[27] However, because the evolution of the disease is very fast because of the progressive motor neuron loss, which in the severest forms, may occur within days or weeks, parents are asked to make a rapid and definitive decision regarding treatment. As a result, they are under huge stress because the consequences of their decisions at this point usually seem to be for life.[38,39] An important issue to discuss concerning treatment is that some might concern long-lasting administration (in the case of *SMN2* modifiers) or might imply a permanent genetic modification (in the case of gene therapy). In addition, there could also be limitations to changing or receiving new treatments in the future.

During the decision-making process, different perspectives should be considered, including patient, family, and physicians' points of view[12,40-43] (Figure 3). Family counseling should cautiously include therapeutic options and limited available clinical trial data, such as long-term effects, which should be discussed before treatment initiation. The quality-of-life assessment can also vary significantly among clinicians, parents, and patients, and this is also a

matter that requires important discussion throughout the process. Shared decision making to decide on care or treatment is encouraged; however, non-directiveness by the expert should be maintained in the process and palliative care should also be discussed. The health care professional's awareness and experience of an available treatment that the patient is likely to benefit from may influence the parent's decision.[44]

The development of effective SMA therapies will lead to changes in the traditional genetic counseling approach in SMA because early intervention is essential for better outcomes.[19] However, it is of paramount importance to manage the family's expectations because, in some cases, the information available is limited and consensus for relevant outcomes is in the process of being developed. In any case, it is crucial to achieve agreement on outcomes that are relevant for the patient and their family. This should be particularly considered in situations that the information available at other hospitals or countries is different. Patients may find inaccurate information or information aimed at patients from other countries where medical care may be different. Thus, informing about the limited data and the importance of adhering to the standard of care, as well as promoting confidence in multidisciplinary teams, may facilitate the family's treatment decision.

Furthermore, health care providers are facing a patient that has never been treated before and the issues of therapy and concomitant follow-up should contemplate the 3 main aspects of a person described in the biopsychosocial model: the organism itself, the psyche, and the social environment, highlighting that patients place particular importance on the emotional impact of the care experience (Figure 2). There should be a statement to the patient and relatives that therapy does not replace close multidisciplinary follow-up and standard-of-care proactive measures but forms an essential part of them. Indeed, a complex disease such as SMA requires the implementation of integrated and multidisciplinary clinics instead of the traditional monographic consultation. The specialists involved in the follow-up of patients with SMA and their tasks are currently increasing as patients live longer and improve their motor function, whereas their phenotypes evolve into a novel mix of motor function, respiratory, nutritional, and orthopedic features.[12] These new patients with SMA are growing and are expected to live beyond childhood, into adolescence and adulthood, leading us to consider the transition of pediatric patients to adult care (Figure 1). The transition process during adolescence, as previously described in other pathologies, should be gradual so the patient can develop skills to adapt to a new care provision.[45]

Communication of SMA heterozygous carrier status: Impact on reproductive options

A new SMA diagnosis in a family increases the relatives' risk of being heterozygotes and usually implies a cascade of testing to determine their genetic status. On the other hand, population SMA screening may be performed at different levels: preconception, prenatal, or neonatal. As mentioned before, prenatal and neonatal screenings have limitations regarding prognosis because the age of onset cannot be factored in. Generally, screening programs have a high acceptance in the general population; the main reasons for not participating include lack of awareness or a negative family history of the disease, its perceived low incidence, and also economic issues.[46] To assess the clinical usefulness of screening programs, including their impact on reproductive choices, further studies are required.

The American College of Medical Genetics (ACMG) considers that population-based genetic SMA screening is reasonable because of the clinical severity, high heterozygous carrier frequency, known specificity and sensitivity of a single test, and the ability to offer prenatal diagnosis along with genetic counseling. ACMG also considers the clinical usefulness of genetic screening when the test results make it possible to implement an effective treatment. For these reasons, both the ACMG and the American College of Obstetricians and Gynecologists advocate SMA screening for couples considering pregnancy or that are pregnant.[47]

Some countries perform SMA preconception screening in the general population.[19,46] Population-based screening for an *SMN1* deletion is essential to offer reproductive genetic counseling and determine the SMA risk in the offspring. However, for comprehensive communication, residual risks should be discussed with the couple during genetic counseling sessions. The most common molecular defect in the *SMN1* gene is the absence of exons 7 and 8. Quantitative testing reduces the risk of being a heterozygote; however, it can return a false-negative result as around 2-5% of carrier individuals harbor 2 copies of *SMN1* in the same allele and, in consequence, no copies in the other allele (2/0). Additionally, some patients have pathogenic variants that are not detected via quantitative methods.[48] Furthermore, de novo pathogenic variants and germline mosaicism should also be considered, as previously reported.[49,50]

Facing these new therapeutic scenarios, SMA population screening programs will facilitate the identification of heterozygotes at increased risk of having affected offspring.[19,46] The preconceptional context is probably the most favorable moment to make these decisions; however, preconception and newborn screening programs may be considered complementary by some health systems.[51,52] In this context, the implementation of these programs offers great opportunities yet poses several challenges that need to be explored. For example, once an SMA heterozygous carrier status has been confirmed in a given couple, the new treatment scenario may influence reproductive decisions based on the possibility of applying early interventions in a newborn for a better outcome and prognosis.[21] In utero therapy of the disease is beginning to be a potential research area for cases predicted to be severe, such as type 0 and type I.[23,53]

Perspectives and conclusions

Recent advances in SMA therapy and the detection of pre-symptomatic patients are changing the trajectories of the disease but entail a communication challenge for new SMA diagnoses. They also highlight the relevance of adequate communication in these situations, especially because of the need to make urgent decisions concerning the therapeutic options of the patient. Besides the prenatal and newborn screening settings, an adequate strategy for communication of the diagnosis should also be considered in symptomatic cases developed after a false-negative newborn screening, as well as in historical patients with SMA with an increased interest in receiving new therapies (Figure 1). All of these scenarios stress the necessity to guide professionals to perform as a team in order to have a satisfactory communication process for patients with SMA and their families.

Data Availability

No data sets were generated or analyzed during the current study.

Funding

This work was partially funded by grants from the Spanish Instituto de Salud Carlos III, Fondo de Investigaciones Sanitarias and co-funded with ERDF funds (grant no. FIS PI18/000687 to E.F.T.).

Acknowledgments

The authors would like to express their deepest appreciation to all the patients with SMA and their families for their support and trust.

Eduardo F. Tizzano is member of the European Reference Network on Rare Congenital Malformations and Rare Intellectual Disability ERN-ITHACA. [EU Framework Partnership Agreement ID: 3HP-HP-FPA ERN-01-2016/739516].

Author Information

Conceptualization: E.F.T.; Funding Acquisition: E.F.T.; Investigation: E.R.-M., A.A., P.M.-C., E.F.T.; Methodology: E.R.-M., A.A., P.M.-C., E.F.T.; Supervision E.F.T.; Writing-original draft: E.R.-M, E.F.T.; Writing-review & editing: E.R.-M., A.A., P.M.-C., M.C.-S., E.B., M.L., B.T.D., E.F.T.

ORCIDs

Eulàlia Rovira-Moreno: https://orcid.org/0000-0001-5483-7031
Anna Abulí: https://orcid.org/0000-0001-9894-0639
Patricia Muñoz-Cabello: https://orcid.org/0000-0002-5242-9605
Marta Codina-Sola: https://orcid.org/0000-0002-5382-413X
Eduardo F. Tizzano: https://orcid.org/0000-0002-7116-6310

Conflict of Interest

The manuscript has been seen and approved by all the authors and they have taken care to ensure the integrity of the work. Eulàlia Rovira-Moreno, Anna Abulí, Patricia Muñoz-Cabello, Marta Codina-Sola, Eva Baillès and Mencía de Lemus have no conflicts of interest or financial disclosures to report.

Basil T. Darras has served as an ad hoc scientific board member for Biogen, Novartis Gene Therapies (AveXis), and Roche and Genentech, the pharmaceutical companies which manufacture nusinersen, onasemnogene abeparvovec-xioi, and risdiplam. Dr. Darras is also the FIREFISH study Steering Committee Chair for Roche, which manufactures risdiplam.

Eduardo F. Tizzano has served as an ad hoc scientific board member for Biogen, Novartis Gene Therapies (AveXis), and Roche, the pharmaceutical companies which manufacture nusinersen, onasemnogene abeparvovec-xioi, and risdiplam, respectively.

References

1. Sugarman EA, Nagan N, Zhu H, et al. Pan-ethnic carrier screening and prenatal diagnosis for spinal muscular atrophy: clinical laboratory analysis of >72 400 specimens. *Eur J Hum Genet*. 2012;20(1):27-32. http://doi.org/10.1038/ejhg.2011.134
2. Finkel RS, McDermott MP, Kaufmann P, et al. Observational study of spinal muscular atrophy type I and implications for clinical trials. *Neurology*. 2014;83(9):810-817. http://doi.org/10.1212/WNL.0000000000000741
3. Munsat TL, Davies KE. Bonn, Germany. Neuromuscul Disord. *International SMA Consortium Meeting*. 1992;2(5-6):423-428. http://doi.org/10.1016/S0960-8966(06)80015-5
4. Talbot K, Tizzano EF. The clinical landscape for SMA in a new therapeutic era. *Gene Ther*. 2017;24(9):529-533. http://doi.org/10.1038/gt.2017.52
5. Kolb SJ, PhD Coffey CS, Yankey JW, et al. Natural history of infantile-onset spinal muscular atrophy. *Ann Neurol*. 2017;82(6):883-891. http://doi.org/10.1002/ana.25101
6. Monani UR, Lorson CL, Parsons DW, et al. A single nucleotide difference that alters splicing patterns distinguishes the SMA gene SMN1 from the copy gene SMN2. *Hum Mol Genet*. 1999;8(7):1177-1183. http://doi.org/10.1093/hmg/8.7.1177
7. Calucho M, Bernal S, Alías L, et al. Correlation between SMA type and SMN2 copy number revisited: an analysis of 625 unrelated Spanish

patients and a compilation of 2834 reported cases. *Neuromuscul Disord*. 2018;28(3):208-215. http://doi.org/10.1016/j.nmd.2018.01.003
8. Lefebvre S, Bürglen L, Reboullet S, et al. Identification and characterization of a spinal muscular atrophy-determining gene. *Cell*. 1995;80(1):155-165. http://doi.org/10.1016/0092-8674(95)90460-3
9. Finkel RS, Mercuri E, Darras BT, et al. Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy. *N Engl J Med*. 2017;377(18):1723-1732. http://doi.org/10.1056/NEJMoa1702752
10. Mendell JR, Al-Zaidy S, Shell R, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. *N Engl J Med*. 2017;377(18):1713-1722. http://doi.org/10.1056/NEJMoa1706198
11. Darras BT, Masson R, Mazurkiewicz-Bełdzińska M, et al. Risdiplam-Treated Infants with Type 1 Spinal Muscular Atrophy versus Historical Controls. *N Engl J Med*. 2021;385(5):427-435. http://doi.org/10.1056/NEJMoa2102047
12. Tizzano EF, Finkel RS. Spinal muscular atrophy: a changing phenotype beyond the clinical trials. *Neuromuscul Disord*. 2017;27(10):883-889. http://doi.org/10.1016/j.nmd.2017.05.011
13. Dangouloff T, Burghes A, Tizzano EF, Servais L, NBS SMA Study Group. ENMC international workshop. 244th ENMC international workshop: newborn screening in spinal muscular atrophy May 10-12, 2019, Hoofdorp, The Netherlands. *Neuromuscul Disord*. 2020;30(1):93-103. http://doi.org/10.1016/j.nmd.2019.11.002
14. Müller-Felber W, Vill K, Schwartz O, et al. Infants diagnosed with spinal muscular atrophy and 4 SMN2 copies through newborn screening – opportunity or burden? *J Neuromuscul Dis*. 2020;7(2):109-117. http://doi.org/10.3233/JND-200475
15. Swoboda KJ. Seize the day: newborn screening for SMA. *Am J Med Genet A*. 2010;152A(7):1605-1607. http://doi.org/10.1002/ajmg.a.33519
16. Yeo CJJ, Simmons Z, De Vivo DC, Darras BT. Ethical perspectives on treatment options with spinal muscular atrophy patients. *Ann Neurol*. 2022;91(3):305-316. http://doi.org/10.1002/ana.26299
17. Cuscó I, Bernal S, Blasco-Pérez L, et al. Practical guidelines to manage discordant situations of SMN2 copy number in patients with spinal muscular atrophy. *Neurol Genet*. 2020;6(6):e530. http://doi.org/10.1212/NXG.0000000000000530
18. Blaschek A, HK OS, et al. Newborn screening for SMA – can a wait-and-see strategy be responsibly justified in patients with four SMN2 copies? *Neuromuscul Disord*. 2022;9(5):597-605.
19. Aharoni S, Nevo Y, Orenstein N, et al. Impact of a national population-based carrier-screening program on spinal muscular atrophy births. *Neuromuscul Disord*. 2020;30(12):970-974. http://doi.org/10.1016/j.nmd.2020.10.005
20. Pieper E, Sexton A, Ryan MM, Forbes R. Communication about spinal muscular atrophy and genetic risk within families: an Australian pilot study. *J Paediatr Child Health*. 2020;56(8):1263-1269. http://doi.org/10.1111/jpc.14915
21. Serra-Juhe C, Tizzano EF. Perspectives in genetic counseling for spinal muscular atrophy in the new therapeutic era: early pre-symptomatic intervention and test in minors. *Eur J Hum Genet*. 2019;27(12):1774-1782. http://doi.org/10.1038/s41431-019-0415-4
22. Tizzano EF, Zafeiriou D. Prenatal aspects in spinal muscular atrophy: from early detection to early presymptomatic intervention. *Eur J Paediatr Neurol*. 2018;22(6):944-950. http://doi.org/10.1016/j.ejpn.2018.08.009
23. Finkel RS, Benatar M. Pre-symptomatic spinal muscular atrophy: a proposed nosology. *Brain*. 2022;145(7):2247-2249. http://doi.org/10.1093/brain/awac125
24. Lazarus R, Folkman S. *Stress, Appraisal, and Coping*. New York: Springer; 1984.
25. Pelentsov LJ, Fielder AL, Laws TA, Esterman AJ. The supportive care needs of parents with a child with a rare disease: results of an online survey. *BMC Fam Pract*. 2016;17(1):88. http://doi.org/10.1186/s12875-016-0488-x
26. von der Lippe C, Diesen PS, Feragen KB. Living with a rare disorder: a systematic review of the qualitative literature. *Mol Genet Genomic Med*. 2017;5(6):758-773. http://doi.org/10.1002/mgg3.315
27. Graungaard AH, Skov L. Why do we need a diagnosis? A qualitative study of parents' experiences, coping and needs, when the newborn child is severely disabled. *Child Care Health Dev*. 2007;33(3):296-307. http://doi.org/10.1111/j.1365-2214.2006.00666.x
28. Zettler B, Estrella E, Liaquat K, Lichten L. Evolving approaches to prenatal genetic counseling for Spinal Muscular Atrophy in the new treatment era. *J Genet Couns*. 2022; June;31(3):803-814. http://doi.org/10.1002/jgc4.1549
29. Havermans T, Tack J, Vertommen A, Proesmans M, de Boeck K. Breaking bad news, the diagnosis of cystic fibrosis in childhood. *J Cyst Fibros*. 2015;14(4):540-546. http://doi.org/10.1016/j.jcf.2014.12.005
30. Gliedt JA, Schneider MJ, Evans MW, King J, Eubanks JE. The biopsychosocial model and chiropractic: a commentary with recommendations for the chiropractic profession. *Chiropr Man Therap*. 2017;25(1):16. http://doi.org/10.1186/s12998-017-0147-x
31. Metcalfe A, Plumridge G, Coad J, Shanks A, Gill P. Parents and children's communication about genetic risk: a qualitative study, learning from families experiences. *Eur J Hum Genet*. 2011;19(6):640-646. http://doi.org/10.1038/ejhg.2010.258
32. Ashtiani S, Makela N, Carrion P, Austin J. Parents' experiences of receiving their child's genetic diagnosis: a qualitative study to inform clinical genetics practice. *Am J Med Genet A*. 2014;164A(6):1496-1502. http://doi.org/10.1002/ajmg.a.36525
33. Pereira-Morales AJ, Adan A, Lopez-Leon S, Forero DA. Personality traits and health-related quality of life: the mediator role of coping strategies and psychological distress. *Ann Gen Psychiatry*. 2018;17(1):25. http://doi.org/10.1186/s12991-018-0196-0
34. Carver CS, Connor-Smith J. Personality and coping. *Annu Rev Psychol*. 2010;61:679-704. http://doi.org/10.1146/annurev.psych.093008.100352
35. Rossi Ferrario SR, Giorgi I, Baiardi P, et al. Illness denial questionnaire for patients and caregivers. *Neuropsychiatr Dis Treat*. 2017;13:909-916. http://doi.org/10.2147/NDT.S128622
36. Gaff CL, Clarke AJ, Atkinson P, et al. Process and outcome in communication of genetic information within families: a systematic review. *Eur J Hum Genet*. 2007;15(10):999-1011. http://doi.org/10.1038/sj.ejhg.5201883
37. Ramos-Platt L, Elman L, Shieh PB. Experience and perspectives in the US on the evolving treatment landscape in spinal muscular atrophy. *Int J Gen Med*. 2022;15(August):7341-7353. http://doi.org/10.2147/IJGM.S369021
38. Kirschner J, Butoianu N, Goemans N, et al. Response to Letter: a Decision for Life – treatment decisions in newly diagnosed families with spinal muscular atrophy. *Eur J Paediatr Neurol*. 2021;30:103-104. http://doi.org/10.1016/j.ejpn.2020.12.005
39. Gusset N, Erbas Y, Germanenko O, Rucinski K, Stumpe E, de Lemus M. European Journal of Paediatric Neurology A Decision for Life – treatment decisions in newly diagnosed families with spinal. *Eur J Paediatr Neurol*. 2021;30:105-107. http://doi.org/10.1016/j.ejpn.2020.11.003
40. Wang CH, Finkel RS, Bertini ES, et al. Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol*. 2007;22(8):1027-1049. http://doi.org/10.1177/0883073807305788
41. Nunlist MM, Blumberg J, Uiterwyk S, Apgar T. UH confidence to improve patient outcomes. Health confidence using. *Fam Pract Manag*. 2016;(6):23 (December):21-24.
42. Lorenzetti RC, Mitch Jacques CH, Donovan C, Cottrell S, Buck J. Managing difficult encounters: understanding physician, patient, and situational factors. *Am Fam Phys*. 2013;87(6):419-425. http://doi.org/10.1016/S0002-838X(13)60075-1
43. Muthuswamy V. Ethical issues in genetic counselling with special reference to haemoglobinopathies. *Indian J Med Res*. 2011;134(4):547-551.
44. Elwyn G, Gray J, Clarke A. Shared decision making and non-directiveness in genetic counselling. *J Med Genet*. 2000;37(2):135-138. http://doi.org/10.1136/jmg.37.2.135
45. Lanzkron S, Sawicki GS, Hassell KL, Konstan MW, Liem RI, McColley SA. Transition to adulthood and adult health care for patients with sickle cell disease or cystic fibrosis: current practices and research priorities. *J Clin Transl Sci*. 2018;2(5):334-342. http://doi.org/10.1017/cts.2018.338

46. Buchanan AH, Lester Kirchner H, Schwartz MLB, et al. Clinical outcomes of a genomic screening program for actionable genetic conditions. *Genet Med*. 2020;22(11):1874-1882. http://doi.org/10.1038/s41436-020-0876-4
47. Zhang J, Wang Y, Ma D, et al. Carrier screening and prenatal diagnosis for spinal muscular atrophy in 13,069 Chinese pregnant women. *J Mol Diagn*. 2020;22(6):817-822. http://doi.org/10.1016/j.jmoldx.2020.03.001
48. Alías L, Barceló MJ, Bernal S, et al. Improving detection and genetic counseling in carriers of spinal muscular atrophy with two copies of the SMN1 gene. *Clin Genet*. 2014;85(5):470-475. http://doi.org/10.1111/cge.12222
49. Ogino S, Wilson RB. Genetic testing and risk assessment for spinal muscular atrophy (SMA). *Hum Genet*. 2002;111(6):477-500. http://doi.org/10.1007/s00439-002-0828-x
50. Campbell L, Daniels RJ, Dubowitz V, Davies KE. Maternal mosaicism for a second mutational event in a type I spinal muscular atrophy family. *Am J Hum Genet*. 1998;63(1):37-44. http://doi.org/10.1086/301918
51. Kirk EP, Ong R, Boggs K, et al. Gene selection for the Australian Reproductive Genetic Carrier Screening Project ('Mackenzie's Mission'). *Eur J Hum Genet*. 2021;29(1):79-87. http://doi.org/10.1038/s41431-020-0685-x
52. Kariyawasam DST, Russell JS, Wiley V, Alexander IE, Farrar MA. The implementation of newborn screening for spinal muscular atrophy: the Australian experience. *Genet Med*. 2020;22(3):557-565. http://doi.org/10.1038/s41436-019-0673-0
53. Baptiste C, De Vivo DC. Spinal muscular atrophy: a potential target for in utero therapy. *Clin Obstet Gynecol*. 2021;64(4):917-925. http://doi.org/10.1097/GRF.0000000000000654