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S Monges, A Rosa

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Management of neuromuscular diseases and spinal muscular atrophy in Latin America

Soledad Monges[1] and Alberto Rosa[2, 3]

[1]Servicio de Neurología, Hospital Nacional de Pediatría Juan P. Garrahan, Buenos Aires, Argentina; [2]Fundacion Allende y Sanatorio Allende, Córdoba, Argentina; [3]IRNASUS-CONICET, Universidad Católica de Córdoba, Argentina.

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Correspondence should be addressed to S.M (mmonges@intramed.net) at:

Soledad Monges (MD)

Servicio de Neurología

Hospital Nacional de Pediatría Juan P. Garrahan

Combate de los Pozos 1881

(C 1245 AAM) C.A.B.A.

+54 11 4122-6000

Argentina

Pr. Alberto L Rosa (MD, PhD)

alberto_l_rosa@yahoo.com.ar

Sanatorio Allende

Obispo Oro 42 7º Piso.

+54 0810 555 2553 –Int.: 1266. Laboratory: 1319

Cordoba

Argentina

Abstract

Latin America (LA) has a population of ~645 million people distributed over 33 countries with marked political, cultural, and economic differences. In LA, patients with inherited neuromuscular diseases (NMD) often do not have access to specialized medical centres and many of them go undiagnosed. General management and care of spinal muscular dystrophy (SMA) patients in the region varies due to heterogeneous health care. An active generation of young clinical neurologists is being trained for the specialized care of SMA and other NM patients, both in the private and public sectors. The Euro-Latin-American Summer School of Myology (EVELAM) as well as efforts of professionals at large public centres in the major cities of LA play a leading role in this development. Different regional academic-scientific organizations as well as the expanding number of Telethon Centres and the creation of parent organizations, mostly concerning SMA, all together are contributing to the increased quality of the management of NMD patients. Over the past years, academic and clinical research, as well as the establishment of qualified centres for the molecular testing of NMD are pushing forward the creation of patient registries and the development of specific clinical trials, with Argentina and Brazil having a major role in this field. Nevertheless, increased awareness and further training of specialized health professionals are necessary to reach patients that are currently lacking care throughout the region.

Introduction

Neuromuscular diseases (NMD) are a heterogeneous group of disorders characterized by involvement of different components of the peripheral nervous system. Spinal muscular atrophy (SMA) is part of this group and is characterized by degeneration of the motor neurons in the anterior horn of the spinal cord. Over the past two decades, knowledge on the disease has greatly increased leading to the development of new treatments (1) and the approval of the promising new drug Spinraza by the F.D.A. (Food and Drug Administration, USA) at the end of 2016.

Latin America (LA), with a current population of around 645 million people, is an extensive and heterogeneous continent, with marked political and cultural differences. This heterogeneity is recognized in the region as a whole, but also within countries. Many patients with SMA and other NMD currently receive no treatment at all. Although in LA exact numbers are unknown, considering the worldwide incidence of SMA - 1 per 6 000-10 000 live births (2, 3) - very probably many patients go undiagnosed. People living in remote rural areas and indigenous communities frequently have limited access to conventional health systems and often consult traditional healers. In contrast, in certain regions, especially in large cities in Argentina, Brazil, Chile, and Mexico, care is comparable to that in major North American and European cities. Referral and counter-referral services in the region are rare.

Major Developments in Neuromuscular diseases in Latin America

Over the past decades, leading clinical neurologists from Argentina, Brazil, and Mexico have been pioneers in the development of diagnostic methods for, and management of patients with NMD in LA. Subsequently, new generations have assumed their role developing specialized care for these patients in private and public centres throughout the continent. The young LA specialists were mostly trained at the annual Summer School of Myology, organized at the

Institute of Myology in Paris since 1998. In addition, since 2007, the Euro-Latin-American Summer School of Myology (EVELAM) is held yearly in different countries of LA with the participation of lecturing local and foreign experts in NMD. The school is attended by 100-150 clinicians and researchers (i.e. neurologists, pathologists, geneticists, physical therapists, etc.) coming from different LA countries. The aim of EVELAM is to disseminate and increase the knowledge and awareness of NMD in the region. Since its beginnings, EVELAM has been an important academic and scientific resource for the training of health professionals involved in the care of patients with NMD (4). Over the years, several clinical studies of LA SMA patients have been published in the Spanish literature (5-17).

Genetic research on NMD, involving linkage analyses and gene characterization studies of large NMD families was initiated in Brazil (18). Subsequently, a growing number of research groups started to work in basic and translational research on SMA and NMD, mostly in Argentina, Brazil, Chile, Mexico, and Uruguay and often in collaboration with centres in Europe. It is expected that these studies will encourage other countries in the region to start specific clinical and research programs regarding NMD.

In Argentina, the first molecular studies of the *SMN1* gene were performed in 1997 at INIMEC-CONICET in Córdoba. At this laboratory, molecular testing of several other NMD and the genetic diagnosis of SMA was performed for patients both in Argentina and neighbouring countries. As part of these studies, a rare point mutation in the *SMN1* gene was recognized in a young type III SMA patient from Argentina (19). In 1998, molecular diagnosis of SMA was started at the molecular diagnosis laboratory at Hospital J.P. Garrahan, a public reference hospital in Buenos Aires, Argentina. At the same time, Brazilian groups also started clinical research in SMA patients (20). Since 2011, *SMN2* copy number and SMA carrier studies have been performed in laboratories in Argentina and Brazil (21).

In 2006, a program was set up for patient care, teaching, and research in NMD at Hospital Garrahan in order to improve the quality of life of SMA patients. A dedicated and trained interdisciplinary team was set up, consisting of a neurologist, physical therapist, pathologist, clinician, geneticist, palliative care specialist, nutritionist, and endocrinologist, among others. The team covers different aspects of the NM patient ranging from diagnosis to transition to adult care and end-of-life palliative care for the patients and their families. The consensus statement for the standard of care in SMA by Wang et al. (22) is used.

Parent organisations, patient registries, and clinical trials in Latin America

Families of patients with different NMD have set up parent organisations. Among them parents of children with SMA founded in 2004 a non-profit association for families of SMA patients in Argentina (FAME; www.fameargentina.com.ar/). FAME-Argentina has participated in yearly international meetings of SMA families - CURE SMA. This parent association has been a strong advocate for and sponsor of the development of early diagnosis, care, and research, allowing for health professionals in the field to attend international meetings and online courses and participating in the organisation of training symposia. Similar parent organisations were created in Brazil, Chile, Mexico, Venezuela, and Uruguay. Between 2008 and 2009, in Argentina FAME locally supported and coordinated "CARNI-VAL" (23), the first pharmacological trial to be held in LA for the treatment of SMA patients. It was a multicentre study coordinated together with the Project Cure SMA including centres in the US, Canada, and Argentina. The protocol included baseline visits and clinical assessments with a total study duration of twelve months. Fourteen patients were enrolled in the trial. In Argentina, some patients had to travel long distances (sometimes more than 1 000 miles) to attend the visits at Sanatorio Allende, in the city of Cordoba. CARNI-VAL led to additional studies on SMA in Argentina.

In 2016, Hospital J.P. Garrahan in Buenos Aires, Argentina, became one of the study sites of Nurture, an open-label study to evaluate the efficacy, safety, tolerability, and pharmacokinetics of multiple intrathecal doses of ISIS 396443 in pre-symptomatic subjects with genetically diagnosed SMA. Currently, the possibility of entering seven more Argentine patients with SMA type 1 into the expanded program is being evaluated.

Another important aim in the care for SMA patients and families in LA was the development of a local registry for patients with NMD. Currently, the Argentine registry includes patients with SMA and DMD as part of TREAT-NMD. These data contributed to a worldwide epidemiological study on SMA (24). Local registries of patients with SMA and NMD that are part of TREAT-NMD exist in Chile and Mexico. An additional a registry is being developed in Brazil.

In the region, Chile has strongly contributed to the local knowledge on NMD by the dissemination of a Spanish version of the SOC-based TREAT-NMD guidelines.

Interestingly, the worldwide-distributed "Telethon" organizations (i.e. a televised fundraising event that lasts many hours or even days) were designed for LA by the Chilean Mario Kreutzberger ("Don Francisco") with the aim to develop services for rehabilitation and social inclusion of children and adolescents with disabilities. The first Telethon was held in Chile in 1978. The interest in and impact of Telethon as a fundraising project to help patients with disabilities quickly expanded to other countries in LA as well as Europe, Canada, and the US. Currently, 12 American countries have Telethon Organisations with 145 rehabilitation centres and support therapy units built in Chile, USA, Colombia, Paraguay, Peru, Puerto Rico, Uruguay, El Salvador, Mexico, Honduras, Nicaragua, and Guatemala. Around 230 000 children, adolescents, and adults with disabilities receive annual assistance through this system in LA. Over the past years, many LA Telethon rehabilitation centres have included a specific program for the study, diagnosis, and physical management of patients with NMD

and their families as well as a specific registry of these patients. The participation of the medical staff from these centres in the annual EVELAMs as well as the biannual meetings of ORITEL contribute to the general awareness and specific care of NM patients and the creation of an LA framework for future qualified medical trials and NM patient follow-up.

In addition to public and private medical centres specialized in NM patients and the activities of EVELAMs and Telethons, there are other academic and scientific organizations with the mission to promote awareness, advancement, diffusion, and research in the field of NMD in LA. Among these, SOLANE (Latin-America Society of Neuromuscular diseases; http://www.websolane.org/) and GrELAM (Euro-Latin American Group of Myology) have relatively recently been created to encourage exchange of scientific information and multidisciplinary collaboration between individuals, organizations, societies, and study groups concerning NMD and related disciplines among countries in the region.

In spite of these efforts in LA, the treatment gap - the difference between people with SMA and NMD and the patients who are actually treated - is still wide. In many countries no specialized care is available. To reach patients throughout the region, adequate training of specialized health professionals is necessary. There is a need to create new awareness of the disease through the organisation of courses for neurologists treating NM patients. In the coming years, national registries in association with the TREAT-DMD should be started in other LA countries. Referral and counter-referral programs should be in place for consultation and possible referral of patients with neuromuscular diseases to tertiary-care centres.

Conclusion

Recently, much has been happening in the field of myology in LA. Many aspects concerning the diagnosis and management of patients, however, remain to be covered. Most important is the training of young myologists who are able to adequately identify individuals with NMD

and deliver cost-effective care. New challenges lie in next-generation sequencing (NGS) (i.e. exome studies and gene panel analyses) and their adequate interpretation associated with clinical findings. Concerning the multidisciplinary management of NM patients, while in some countries specialized follow-up is available, in other countries the resources for appropriate care need to be improved. A referral and counter-referral program should be in place for consultation and possible referral of patients with NMD to tertiary-care centres.

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References

1. Monani UR, De Vivo DC. Neurodegeneration in spinal muscular atrophy: from disease phenotype and animal models to therapeutic strategies and beyond. *Future Neurol;* 2014 Jan 1;9(1):49-65.
2. Cusin V, Clermont O, Gerard B, Chantereau D, Elion J. Prevalence of SMN1 deletion and duplication in carrier and normal populations: implication for genetic counselling. *J Med Genet;* 2003, 40 (4):e39.
3. Alias L, Barcelo MJ, Bernal S, Martinez-Hernandez R, Also-Rallo E, Vazquez C, 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.
4. Newsletter Institute of Myology: http://www.institut-yologie.org/en/newsletter/newsletter

5. Bueno KC, Gouvea SP, Genari AB, Funayama CA, Zanette DL, Silva WA Jr, et al. Detection of spinal muscular atrophy carriers in a sample of the Brazilian population. *Neuroepidemiology*; 2011. 36, 105-8.
6. Acevedo López AM, Zaldívar Vaillant T, Moreno F, Hernández-Chico C. Atrofia muscular espinal infantil. Introducción del diagnóstico molecular en Cuba. Rev *Cubana Obstet Ginecol*; 1998;25(2):128-34
7. Garófalo Gómez N, Zaldívar Vaillant T, Vargas Díaz J, Rojas Massipe E, Novoa López L. Atrofia muscular espinal en el niño. *Rev Cubana Pediatr*; 2009 v.81 n.3 Ciudad de la Habana jul.-sep.
8. Camacho Plasencia CA. Enfermedad de Werdnig-Hoffman: a proposito de un caso con estadia prolongada. *Rev Haban Cienc Méd*; 2009v.8 n.1 Ciudad de La Habana ene.-mar.
9. Cantarelli dos Santos D, Maia Cavali PT, Mello Santos MA, Antonelli Lehoczki M, Junqueira Rossato A, Landim E. Tratamento cirúrgico da escoliose em pacientes com amiotrofia espinhal com parafusos pediculares (instrumental de 3ª geração) e complicações precoces. *Coluna/Columna*; 2010;9(2):98-103
10. Castiglioni C, Levicán J, Rodillo E, Garmendia MA, Díaz A, Pizarro L, et al. Atrofia muscular espinal: Caracterización clínica, electrofisiológica y molecular de 26 pacientes. *Rev Med Chile*; 2011; 139: 197-204
11. Munhoz da Rocha LE, Pudles E, Bonotto lampert H. Avaliação dos resultados do tratamento cirúrgico da escoliose na atrofia muscular espinhal tipo 2. *Coluna/Columna*; 2011 vol.10 no.3 São Paulo
12. Zaldívar Vaillant T, Garófalo Gómez N, Vargas Díaz J, Rojas Massipe E, Novoa López LM, Bermúdez Linares V. Frecuencia de algunas enfermedades genéticas en Neuropediatría. *Revista Cubana de Pediatría*; 2012; 84(2):368-374

13. Viñas CI, Martín I, Zaldivar V T, Garófalo N, Zayas M, Guerra R, et al. Análisis genético molecular en Atrofia Muscular Espinal. *Rev Chil Pediatr*; 2013; 84 (5): 499-504

14. Rodríguez I, Fuentes C, Rivas C, Fernanda Molina R, Constanza Sepúlveda C, Daniel Zenteno A. Rehabilitación respiratoria en el paciente neuromuscular: efectos sobre la tolerancia al ejercicio y musculatura respiratoria. Resultado de una serie de casos. Rev. *Chil Enferm Respir*; 2013. vol.29 no.4 Santiago

15. Valencia HD, Rendón Muñoz J, Pineda N, Ortiz B, Montoya JH, Cornejo JW. Características clínicas de los pacientes menores de 18 años con atrofia muscular espinal en Medellín. *Acta Neurol Colomb*; 2016; 32(1):9-17

16. Freire Magalhães PA, Gusmão d´Amorim AC, Mendes AP, Albuquerque Ramos ME, Santos de Almeida LB, Menezes Bezerra Duarte MC. Dispositivos ventilatórios não invasivos em criança portadora de amiotrofia espinhal do tipo 1: relato de caso. Rev. Bras. *Saúde Matern Infant*; 2015, Recife, 15 (4): 435-440

17. Zárate-Aspiros R, Rosas-Sumano AB, Paz-Pacheco A, Fenton-Navarro PA, Chinas-López S, López-Ríos J.A. Case report: type I spinal muscular atrophy: Werdnig-Hoffmann disease. *Boletín médico del Hospital Infantil de México*; 2013, Vol.70 (1) ene./feb.

18. Zatz M, de Paula F, Starling A, Vainzof M. The 10 autosomal recessive limb-girdle muscular dystrophies. *Neuromuscul Disord*; 2003, 13, 532-44.

19. Alías L, Bernal S, Fuentes-Prior P, Barceló MJ, Also E, Martínez-Hernández R, et al. Mutation update of spinal muscular atrophy in Spain: molecular characterization of 745 unrelated patients and identification of four novel mutations in the SMN1 gene. *Hum Genet*; 2009. 125, 29-39.

20. Kim C.A, Passos-Bueno M.R, Marie S.K, Cerqueira A, Conti U, Marques-Dias M.J, Gonzalez C.H et al. Clinical and molecular analysis of spinal muscular atrophy in Brazilian patients. *Gen Mol Biol;* 1999, Vol 22 (4). On-line version ISSN 1678-4685

21. Medrano S, Monges S, Gravina LP, Alías L, Mozzoni J, Aráoz HV, et al. Genotype-phenotype correlation of SMN locus genes in spinal muscular atrophy children from Argentina. *Eur J Paediatr Neurol*; 2016, Nov;20(6):910-917.

22. Wang CH, Finkel RS, Bertini ES, Schroth M, Simonds A, Wong B, et al; Participants of the International Conference on SMA Standard of Care. Consensus statement for standard of care in spinal muscular atrophy. *J Child Neurol*; 2007 Aug; 22(8):1027-49.

23. Swoboda KJ, Scott CB, Crawford TO, Simard LR, Reyna SP et al. SMA CARNI-VAL trial part I: double-blind, randomized, placebo-controlled trial of L-carnitine and valproic acid in spinal muscular atrophy. *PLoS One*; 2010, 5(8):e12140. doi: 10.1371/journal.pone.0012140.

24. Bladen CL, Salgado D, Monges S, Foncuberta ME, Kekou K, Kosma K, et al. The TREAT-NMD DMD Global Database: analysis of more than 7,000 Duchenne muscular dystrophy mutations. *Hum Mutat*; 2015 Apr;36(4):395-402. doi: 10.1002/humu.22758.