Arch Argent Pediatr 2023;121(2):e202202946

Diagnostic delay in rare diseases

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Spinal muscular atrophy (SMA) is a progressive neuromuscular disease of autosomal recessive inheritance and variable severity. In a series of Argentine children, the most severe forms of SMA developed into chronic respiratory failure at 4 months and a median survival of 6 months.[1] Until a few years ago, the treatment of SMA, with an estimated incidence of 1/6000 to 1/10 000 live births, was exclusively supportive.

In 2019, nusinersen, the first specific treatment for SMA, which had been available in the United States, Canada, and Europe since 2016, was approved in Argentina. Over time, 2 other therapeutic options were introduced: onasemnogene and risdiplam, with different mechanisms of action. Any of these should be administered within a treatment program that follows the recommended standards of health care for SMA.[2,3] Notwithstanding the latter, the central aspect of any of the aforementioned regimens is that their indication and effectiveness depend, to a large extent, on the early diagnosis of SMA.[4] The possibility of a child achieving important motor developmental milestones, such as sitting and even the possibility of walking independently, is at stake in an early diagnosis and treatment.

Affected families and patients must deal not only with the difficulty of delayed diagnosis, but also with that of having access to timely and appropriate treatment, trained health care staff and funding from the various health care providers. This is probably a problem common to other rare diseases. The critical question is how to improve the process of diagnosis and treatment of this type of diseases to achieve the best result for the patient. Different strategies have been proposed, such as those related to the education of pediatric specialists and community outreach campaigns.[5] In recent years, the emergence of specific treatments has been accompanied by increased availability for molecular diagnosis.

The study by Bolaño Díaz et al.,[6] addresses the problem of delayed SMA diagnosis in our country. The authors suggest that the leading cause is an absent index of suspicion by both pediatricians and neurologists to whom the patients were referred. The range of delay between the onset of symptoms and diagnostic confirmation becomes wider as the severity of the clinical form decreases. It would be interesting to know the origin of the population included and whether there are also regional differences in such diagnostic delay. In addition, it is worth

doi: http://dx.doi.org/10.5546/aap.2022-02946.eng

To cite: Aguerre V. Diagnostic delay in rare diseases. *Arch Argent Pediatr* 2023;121(2):e202202946.

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noting that, outside the studied population, there is probably a significant number of children who died without having a diagnostic confirmation.

In recent years, some countries have introduced the diagnosis of SMA in the neonatal screening, allowing the treatment of patients in the pre-symptomatic stage, an ideal situation given the severity of SMA. These countries include, among others, Australia, Belgium, Canada, United States, Germany, Italy, Japan, and Taiwan.[7]

In Argentina, the National Commission for Patients with Spinal Muscular Atrophy (Comisión Nacional para Pacientes con Atrofia Muscular Espinal, CONAME) was created in 2020, within the scope of the National Program for Rare Diseases of the National Ministry of Health. In January 2021, nusinersen, a very expensive drug, was added to protected technologies. CONAME is responsible for determining whether patients without health insurance coverage through a labor union or private company, who are admitted to the Registry of Protected Technologies and request coverage, meet the requirements and conditions to receive the treatment. However, the time that elapses between diagnosis, therapeutic indication, and the actual initiation of treatment is still prolonged, which is detrimental to its effectiveness, especially in the most severe forms of SMA.

A strength of the study by Bolaño Díaz et al.,[6] is that of making the complex situation of the diagnosis of SMA in Argentina visible and disseminating the clinical bases for clinical suspicion. It is worth remembering that "What is not known or what is not thought of goes undiagnosed, which is almost always because it is not well known." An early diagnosis is the first step on a path that must be efficiently followed to achieve the best possible outcome for each patient. ■

REFERENCES

1. Aguerre V, De Castro F, Mozzoni J, Gravina LP, et al. Natural history of type 1 spinal muscular atrophy in a series of Argentinian children. *J Neuromuscul Dis*. 2020; 7(4):453-8.
2. Mercuri E, Finkel RS, Muntoni F, Wirth B, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. *Neuromuscul Disord*. 2018; 28(2):103-15.
3. Monges S, De Castro Perez F, Mozzoni J, Aguerre V, et al. Manejo de la Atrofia Muscular Espinal. [Accessed on: December 3rd, 2022]. Available at: https://www.garrahan.gov.ar/images/intranet/guias_atencion/GAP_2019_-_MANEJO_AME_-_VERSION_FINAL.pdf
4. Baranello G, Gorni K, Daigl M, Kotzeva A, et al. Prognostic factors and treatment-effect modifiers in spinal muscular atrophy. *Clin Pharmacol Ther*. 2021; 110(6):1435-54.
5. Cao Y, Cheng M, Qu Y, Bai J, et al. Factors associated with delayed diagnosis of spinal muscular atrophy in China and changes in diagnostic delay. *Neuromuscul Disord*. 2021; 31(6):519-27.
6. Bolaño Díaz CF, Morosini M, Chloca F, Mesa L, et al. El difícil camino al diagnóstico del paciente con atrofia muscular espinal. *Arch Argent Pediatr* 2023;121(2):e202102542.
7. Dangouloff T, Vrščaj E, Servais L, Osredkar D; SMA NBS World Study Group. Newborn screening programs for spinal muscular atrophy worldwide: Where we stand and where to go. *Neuromuscul Disord*. 2021; 31(6):574-82.