

Differences in rectoanal inhibitory reflex duration between patients with refractory functional constipation and myelomeningocele

Julián Fernández^a, Gabriela Messere^a, Gonzalo Ortiz^a, Adriana Oviedo^a, Jorge Vidal^a, Silvia Morise^a, Samuel Nurko^b, Román Bigliardi^a

ABSTRACT

Introduction. Usually, during anorectal manometry, only the presence or absence of rectoanal inhibitory reflex (RAIR) is investigated. Studies have reported that a detailed analysis may provide data of interest. Our hypothesis is that RAIR measurement may provide information to detect organic causes (tethered cord, lipoma, etc.) in patients in whom a functional cause had been previously considered.

Objectives. To compare RAIR duration in anorectal manometry between patients with refractory functional constipation (RFC) and myelomeningocele (MMC).

Population and methods. Observational, analytical, cross-sectional study (2004–2019). Patients with chronic constipation and functional and organic fecal incontinence (myelomeningocele). The anorectal manometry was performed with a water-perfused system, and the duration of RAIR was measured with different volumes (20, 40, and 60 cc). Group 1 (G1): 81 RFC. Group 2 (G2): 54 MMC. Patients with developmental delay, compliant anal sphincter, sacral agenesis and non-cooperative patients were excluded.

Results. A total of 135 individuals were included (62 were male). Their median age was 9.57 years in G1 and 9.63 years in G2. Average duration in G1 versus G2 with 20 cc: 8.89 versus 15.21 seconds; 40 cc: 11.41 versus 21.12 seconds; 60 cc: 14.15 versus 26.02 seconds.

The difference in RAIR duration with the varying volumes was statistically significant ($p = 0.0001$).

Conclusion. RAIR duration was longer with increasing balloon inflation volumes in both populations. RAIR duration was longer in patients with MMC than in those with RFC. Spinal injury should be ruled out in patients with prolonged RAIR.

Key words: pediatrics; manometry; reflex; constipation; myelomeningocele.

doi: <http://dx.doi.org/10.5546/aap.2022-02598>.eng

To cite: Fernández J, Messere G, Ortiz G, Oviedo A, et al. Differences in rectoanal inhibitory reflex duration between patients with refractory functional constipation and myelomeningocele. *Arch Argent Pediatr* 2023;121(2):e202202598.

^a Department of Pediatric Gastroenterology. Hospital Nacional Profesor Alejandro Posadas, El Palomar, Argentina; ^b Center for Motility and Functional Gastrointestinal Disorders, Boston Children's Hospital, Harvard Medical School, Boston, United States.

Correspondence to Román Bigliardi: rnbigliardi@gmail.com

Funding: None.

Conflict of interest: None.

Received: 2-8-2022

Accepted: 7-19-2022



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INTRODUCTION

The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) has defined *constipation* as a “delay or difficulty in defecation present for 2 or more weeks, which causes significant distress to the patient.”¹

Constipation is the reason for consultation in 3% to 5% of visits to the pediatrician and up to 35% of visits to the pediatric gastroenterologist.^{2,3} Fecal incontinence is usually also present in children with constipation (up to 80% of incontinent patients also have constipation).

The prevalence of functional constipation ranges from 20% to 30%.^{4,5}

Continence is maintained by the action of the sphincter apparatus, made up of the internal anal sphincter (IAS), which is innervated by the autonomic nervous system (ANS) and the enteric nervous system (ENS), and the external anal sphincter (EAS), which is innervated by the pudendal nerves. The IAS is composed of smooth muscle and is responsible for 80% of the tone of the anal sphincter at rest, which is mostly of myogenic or involuntary nature. The EAS is striated muscle and allows for the voluntary contraction by sacral stimulation (S2–S4); it is the urgency sphincter.⁶

When stool reaches the rectum causing its distention, the rectoanal inhibitory reflex (RAIR) is induced, resulting in relaxation of the internal anal sphincter. The RAIR may be induced by inflating a rectal balloon and recording the anal response

(negative deflection of anal pressure) by anorectal manometry (*Figure 1*).⁷

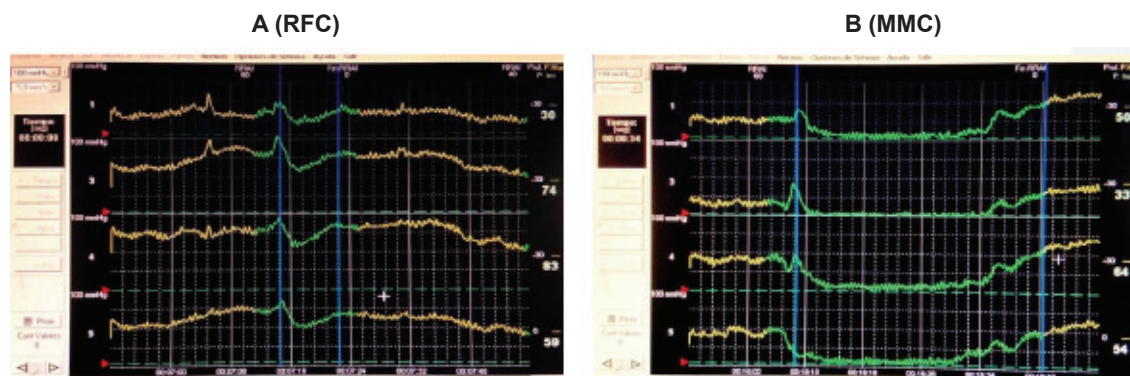
Myelomeningocele is a birth defect of the neural tube, which affects the distal rather than the proximal spinal cord, resulting in an alteration of the vertebral fusion and adjacent skin. According to the National Registry of Congenital Anomalies (Registro Nacional de Anomalías Congénitas de Argentina, RENAC), in Argentina, the prevalence of neural tube defects in the public sector was 9.71/10 000 in 2020.⁸

Neurological and orthopedic involvement is conditioned by the level of the injury and the degree of myelodysplasia. Colorectal and urinary disorders are common in children with myelomeningocele. These patients may develop defecation disorders that are caused by alterations in colorectal motility, decreased anorectal sensitivity, and anal sphincter dysfunction. They also have decreased mobility and often lack adequate bathroom facilities; in addition, their parents—and sometimes physicians—have little information.⁹

The bibliography includes little information about the characteristics of RAIR and there are no studies on validated values in terms of RAIR duration.^{10,11} Knowing the role of the ENS and the ANS in the innervation of the IAS, which is still controversial at present, may significantly contribute to establishing new strategies and therapeutic approaches in the management of patients with chronic constipation and incontinence.

Our hypothesis is that there is an alteration in

FIGURE 1. Tracings showing the duration of the rectoanal inhibitory reflex at 5 mmHg/s of speed and 60 cc of air volume. Figure 1A shows duration in a patient with refractory functional constipation; Figure 1B shows duration in a patient with myelomeningocele. The segment depression caused by the rectoanal inhibitory reflex is observed between the blue lines. A statistically significant difference was observed when comparing both groups



RFC: refractory functional constipation; MMC: myelomeningocele.

the characteristics of the RAIR, secondary to an ANS anomaly due to spinal lesion in patients with MMC, and that the reflex is present in all of them because the ENS is not affected.

OBJECTIVE

Our objective was to compare RAIR duration in anorectal manometry between patients with RFC and MMC.

POPULATION AND METHODS

This was an observational, analytical, cross-sectional study conducted between April 2004 and April 2019.

This study included 135 patients with intractable chronic constipation and fecal incontinence seen at a public hospital in Argentina (Department of Pediatric Gastroenterology of Hospital Nacional Profesor Alejandro Posadas), in whom an anorectal manometry was performed. They were divided into 2 groups:

- Group 1 (G1): 81 patients with RFC.
- Group 2 (G2): 54 patients with MMC older than 6 years old with non-compliant anal sphincter and without developmental delay.

Among the patients attending the MMC clinic and the Department of Pediatric Gastroenterology, patients were selected by convenience based on a previous trial, taking into account that those with tonic sphincter and an adequate cognitive level would be able to follow the instructions and benefit from biofeedback.¹²

Inclusion criteria: patients with chronic constipation and fecal incontinence older than 6 years.

Exclusion criteria: developmental delay, compliant anal sphincter on inspection, sacral agenesis, and non-collaborative patients.

Anorectal manometry

Manometries were performed using a STA 01 manometer with water-perfused system and nitrogen pump with 6 perfusion channels. A latex-free balloon catheter with 4 radial channels was used. The patient was placed on the left lateral recumbent position.

The RAIR was defined as a drop in the anal canal resting pressure with the observation of a plateau or decline in the recording, with a drop greater than or equal to 5 mmHg, which then returns to basal pressure values.⁷ The RAIR was measured by inflating and deflating the rectal balloon in 2 seconds using 20, 40, and 60 cc.

Definitions

Refractory functional constipation was defined as constipation without an organic cause and not responding to usual treatments for a period of 3 months (diet, habits, laxatives, and enemas).

Functional constipation was defined based on the Rome III criteria for patients treated until 2016 and the Rome IV criteria from that date onwards.

According to the Rome IV criteria for the diagnosis of functional constipation in children older than 4 years, 2 or more criteria must be present at least once per week for at least 1 month, with insufficient symptoms to fulfill the diagnostic criteria of irritable bowel syndrome.

1. Two or fewer defecations per week in a child aged 4 years and older.
2. At least 1 episode of fecal incontinence per week.
3. History of retentive posturing.
4. History of painful or hard bowel movements.
5. Presence of a large fecal mass in the rectum.
6. History of large-diameter stools that may obstruct the toilet.

After a comprehensive assessment, the symptoms cannot be attributed to another medical condition.¹³

An X-ray or MRI of the lumbosacral spine was done in all patients with functional constipation to rule out spinal cord malformations. An anorectal manometry is performed only in patients with functional constipation if it is intractable.

The study was approved by the Bioethics and Research Committee of Hospital Nacional Profesor Alejandro Posadas. Protocol registration code at the Clinical Research Protocol Assessment Commission (*Comisión Evaluadora de Protocolos de Investigación Clínica*, CEPIC), ref.: 224 LUPOSO/18. No informed consent was obtained because this was a retrospective data collection study, with protection of the study subject information (as mentioned in the documentation submitted to the Bioethics and Research Committee).

Statistical analysis

Qualitative variables are summarized with their absolute and percentage frequency. Quantitative variables are expressed based on their distribution with mean and standard deviation (SD) (for those with a normal distribution) and median and interquartile range (for those without normal distribution).

The groups were compared using a χ^2 test or

Fisher's test, based on assumptions for qualitative variables. The Friedman test was used to assess the difference in RAIR duration at 20, 40, and 60 cc of air for patients with RFC and MMC, whereas the Mann-Whitney test was used to assess RAIR duration at a fixed volume.

The risk analysis for having spinal injury based on RAIR duration was performed using odds ratio and its confidence interval (CI) for cutoff points of 1 and 2 standard deviations.

RESULTS

In total, 135 patients were included; 81 (60%) had RFC and 54 (40%) had MMC; 55/81 of those with RFC and 27/54 of those with MMC were male.

The median age in both groups was similar. G1: 9.57 years (1 to 18 years). G2: 9.63 years (5 to 16 years) ($p = 0.3$).

Spinal injury in patients with MMC was located at the thoracic level in 4 (7.4%); high lumbar level in 4 (7.4%); mid lumbar level in 17 (31.5%); low lumbar level in 17 (31.5%); and sacral level in 12 (22.2%).

Manometry results

The main manometry characteristics of patients with MMC are shown in *Table 1*. There were no statistical differences between high and low spinal level for resting pressure, maximum

contraction pressure, and RAIR duration.

The manometry characteristics of patients with RFC are shown in *Table 2*.

All patients in G1 (n: 81) and G2 (n: 54) had a positive RAIR.

The average RAIR duration with the different volumes used in both groups is shown in *Table 3*.

A statistically significant difference in RAIR duration was observed between G1 and G2 ($p = 0.0001$) (*Figure 1*).

Significant differences in reflex duration were observed with increasing volume measurements in each group ($p < 0.0001$) (*Figure 2*).

The association between a longer RAIR duration in relation to 1 and 2 SDs from the value in RFC patients was statistically significant for the presence of spinal injury, with a cutoff point for both +1 SD and +2 SDs from the mean value in patients with functional constipation (mean = 11.41 seconds) and an OR value of 76.47 (CI: 19.77–295.8) and 86.78 (CI: 10.95–687.4), respectively.

DISCUSSION

Our working group is one of the first to compare patients with functional constipation and patients with MMC, and we have demonstrated that RAIR duration is significantly longer in patients with MMC. We included patients with constipation as a control group; the study could

TABLE 1. Results of anorectal manometry in patients with myelomeningocele by spinal injury level and in patients with refractory functional constipation

| | MMC Spinal level// | | P value* | RFC Med (1Q;3Q) |
|-------------------------------|-----------------------|--------------------|----------|--------------------|
| | High Med (1Q;3Q) | Low Med (1Q;3Q) | | |
| Resting pressure (mmHg) | 35 (22.98–48.75) | 38 (32.5–42) | 0.741 | 44 (37–53) |
| Squeeze pressure (mmHg) | 50.5 (8–72) | 44 (36.5–77.5) | 0.436 | 96 (72–109.5) |
| Duration (seconds) with 40 cc | 18 (0–22) | 16 (10.5–24.5) | 0.759 | 11.5 (8.25–13) |

//High (T, L1, L2, L3); low (L4, L5, S).

Med (1Q;3Q): median and difference between first and third quartiles.

*Mann Whitney test, statistically significant P value < 0.05.

MMC: myelomeningocele.

RFC: refractory functional constipation.

TABLE 2. Characteristics of anorectal manometry in patients with refractory functional constipation

| Resting pressure (mmHg) | Squeeze pressure (mmHg) | Duration (seconds), with 40 cc |
|-------------------------|-------------------------|--------------------------------|
| 44 (37–53) * | 96 (72–109.5) * | 11.5 (8.25–13) * |

* Med (1Q;3Q): median and difference between first and third quartiles.

TABLE 3. Duration of rectoanal inhibitory reflex with increasing volumes in both groups

| Volume | Study groups | | P value* |
|-----------|--------------------|--------------------|----------|
| | RFC Med (1Q;3Q) | MMC Med (1Q;3Q) | |
| 20 cc | 8 (7-17) | 15 (12.5-17) | < 0.001 |
| 40 cc | 11.5 (8.25-13) | 18.5 (15.25-24) | < 0.001 |
| 60 cc | 14 (10-17) | 24 (18.25-29.75) | < 0.001 |
| P value** | < 0.001 | < 0.001 | |

Med (1Q;3Q): median and difference between first and third quartiles.

* Mann Whitney test. ** Friedman test. Statistically significant P value < 0.05.

RFC: refractory functional constipation.

MMC: myelomeningocele.

not be performed in healthy patients for ethical reasons.

All our patients with MMC have a positive RAIR, with a longer duration in most of them. The reflex is present because the ANS is undamaged, and the prolonged RAIR duration may be due to a damaged ANS, either by the condition itself or because of surgery.

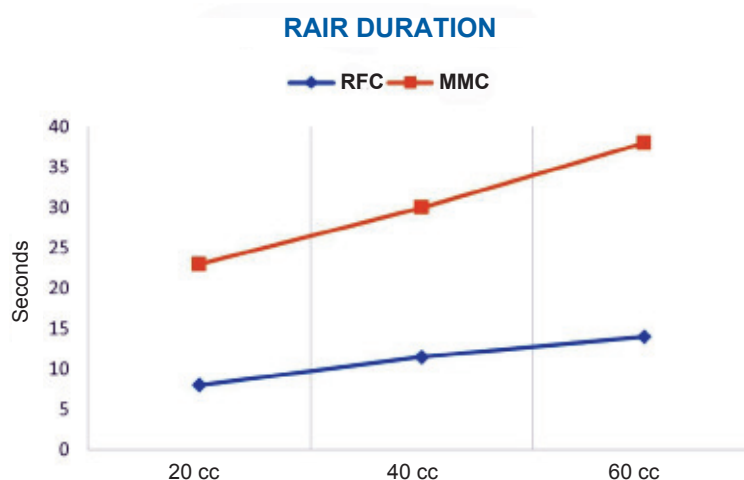
Our findings are similar to those reported in other studies which have also suggested that the ENS is responsible for the presence of the RAIR and modulation depends on the ANS.^{14,15}

Thiruppathy's group studied anorectal physiology in patients with multiple sclerosis and spinal cord lesion and found that constipation was associated with decreased relaxation and

that fecal incontinence correlated with prolonged RAIR duration.¹⁶⁻¹⁸

In an article by Guinet et al, with increasing rectal balloon volumes, the extent and duration of the RAIR were greater for patients with constipation and incontinence, as observed in our study.¹⁹ In another publication, those authors concluded that, although the RAIR is always present, its modulation seems to be altered in patients with multiple sclerosis.²⁰

In another interesting article published by the groups of Rachel Rosen and Samuel Nurko, the prevalence of abnormalities in the MRI of the spinal cord in patients with intractable constipation was 9%; for this reason, we decided to perform a MRI or X-ray of the lumbosacral

FIGURE 2. Rectoanal inhibitory reflex duration based on inflated volume in both populations

RAIR: rectoanal inhibitory reflex.

RFC: refractory functional constipation.

MMC: myelomeningocele.

spine in all of our patients.²¹

We also observed that the presence of spinal lesion was associated with a longer RAIR duration, which was statistically significant; this suggests it is a useful biomarker of spinal impairment in patients previously considered as having intractable functional constipation. As the mean duration of RAIR in RFC is 11.41 seconds, we consider that spinal lesion should be investigated when RAIR duration exceeds 14.8 seconds (1 SD) and 18.1 seconds (2 SDs).

Our findings may be useful to determine which patients may benefit from different treatments, such as biofeedback, rectal irrigation, sacral neuromodulation (percutaneous or surgical), or posterior tibial nerve neurostimulation, but this requires further research.

The strength of our study is that we are the first group to compare RAIR duration between patients with MMC and a group of patients with functional constipation. Also, another remarkable point is the large number of patients studied.

One of the limitations of our study is that we have few patients with a high-level spinal lesion because most of our patients with MMC have a low-level lesion; therefore, we cannot compare sphincter behavior based on lesion level.

Also, it is worth clarifying that the extent of the confidence interval may be due to the sample size.

CONCLUSION

- All patients with MMC had a positive RAIR.
- RAIR duration was longer with increasing balloon inflation volume in both populations.
- RAIR duration was longer in patients with MMC than in those with RFC.
- Spinal lesion should be ruled out in patients with prolonged RAIR.

Acknowledgments

We would like to thank Marcela Mariano, B.S., from the Department of Research and Teaching of Hospital Nacional Prof. Alejandro Posadas, who was in charge of the statistical analysis for the study.

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