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CASE REPORT

ASSOCIATION BETWEEN VESICURETERAL REFLUX AND CHROMOSOME 22 RING ANOMALY - CASE REPORT

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Abstract

Vesicoureteral reflux (VUR) is characterized by retrograde urine flow, caused by impaired occlusion of the intramural portion of the ureter by contraction of the detrusor muscle during urination or secondary to altered bladder dynamics, ureteral obstruction and neuromuscular diseases, such as Phelan-McDermid syndrome. This syndrome is a rare and underreported disease, resulting from the formation of chromosome 22 in a ring and has VUR as its main urological manifestation. The objective of this study is to alert the medical community about one of the differential diagnoses in the VUR etiology, based on the case of a female patient, 4 years and 2 months old, referred to the Pediatric Surgery service of the Mário Covas State Hospital with recurrent infection of urinary tract associated with impaired renal function and bilateral VUR evidenced on cystourethrography. During investigation, the phenotypic findings encouraged the performance of a karyotype that confirmed the alterations found in Phelan-McDermid syndrome. VUR early diagnosis was essential to establish the appropriate therapy, which involved clinical and surgical approaches aimed at improving quality of life, preserving the renal parenchyma and preventing further future complications.

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INTRODUCTION

Vesicoureteral reflux (VUR) is characterized by the retrograde flow of urine, caused by a defect in the occlusion of the intramural portion of the ureter, due to detrusor muscle contraction during urination or secondary to altered bladder dynamics, ureteral obstruction and neuromuscular diseases, resulting from chromosomal changes. VUR tends to be asymptomatic, but facilitates the rise of bacteria to the upper urinary tract, and it is commonly associated with recurrent urinary tract infections (UTIs)^{1,2,3}.

Phelan-McDermid syndrome (PMS) results from the formation of a ring by chromosome 22, the diagnosis of which initially manifests itself as neurodevelopmental disorders, such as autism spectrum disorder and intellectual disability. Signs suggestive of the syndrome include neonatal hypotonia, varied facial dysmorphisms (dolichocephaly, full eyelids and cheeks, bulbous nose with wide nasal bridge and prominent ears) and changes in the body limbs^{4,5}. Furthermore, the main urological alteration of the syndrome is VUR. Even though this association is a common manifestation, it is rarely found in the literature, since this is a rare and underreported syndrome, due to the lack of clinical diagnostic criteria and the need for high-cost exams to complement the investigation⁶⁻⁹.

Therefore, this case report aims to alert the medical community about one of the differential diagnoses in the etiology of VUR, frequently found in autistic patients or those with intellectual disabilities, in order to promote a better quality of life for these children through early multidisciplinary intervention.

CASE REPORT

LOA, 4 years and 2 months, female, first child of non-consanguineous parents, born by cesarean section with a GA of 39 weeks and 1 day, weighing 3,075 g, 47 cm in height and 35.5 cm in head circumference. She was discharged from the maternity ward within the expected time, without complications.

She was referred to the Pediatric Surgery service at Mário Covas State Hospital due to a recurrent UTI. At the time, she had external voiding cystourethrography (CUG) exams with vesicoureteral reflux grade V on the left and grade IV on the right. Furthermore, the physical examination revealed phenotypic characteristics of PMS such as dolichocephaly, full eyebrows, swollen eyelids, wide nasal bridge, bulbous nose and large cheeks. The child had difficulty in language skills but interacted with the medical team. Upon physical examination, there was a depression in the sacral spine with a normal gluteal fold. She had PMS confirmed with G-banding peripheral blood karyotyping, which showed ring chromosome 22 in all metaphases (46, XX, p11.2q13.3) (Figure 1).

We ordered test to investigate this repeat UTI. Ultrasonography of kidneys and urinary tract with right kidney measuring 7.7 cm in length, parenchymal thickness (PE) 0.9 cm with discrete/moderate pyelocaliceal and proximal ureteral dilation; left kidney 8.2 cm long, EP 0.7 cm with marked pyelocaliceal and

ureteral dilation throughout it. At Static Renal Scintigraphy (DMSA) (Figure 2): the right kidney has 68% of its tubular function and the left 32% with reduced volume and image amputation in the lower renal pole, suggestive of renal scarring. Dynamic Renal Scintigraphy (DTPA) revealed no evidence of functional obstruction. The urodynamic study showed as overactive bladder and dysfunctional urination.

Based on the test results, she was initially treated with anticholinergics and alpha blockers. During follow-up for almost two years, there was worsening of the loss of the renal parenchyma assessed by DMSA scintigraphy and we decided to perform bilateral vesico-ureteral reimplantation using the Politano-Leadbetter technique.

The patient is currently in good postoperative condition, with no recurrence of her urinary infections.

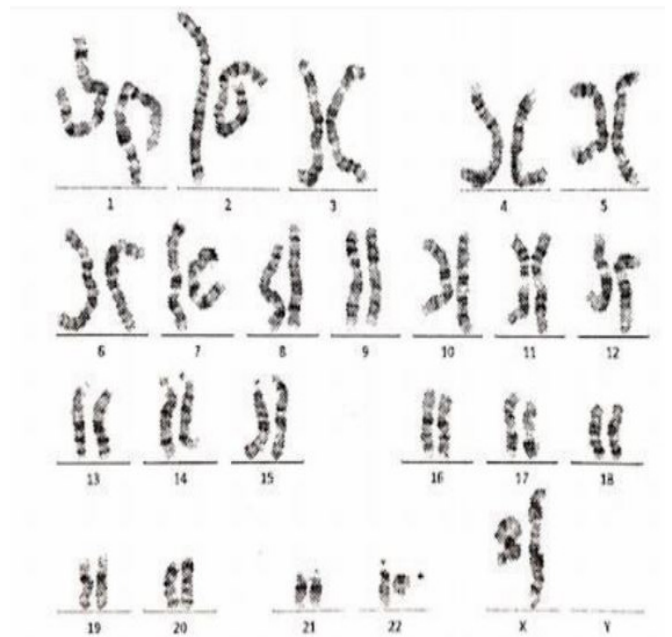


Figure 1. Peripheral blood karyotype with G banding that resulted in 46, XX, r(22)(p11.2q13.3) and ring chromosome 22 in all metaphases analyzed.

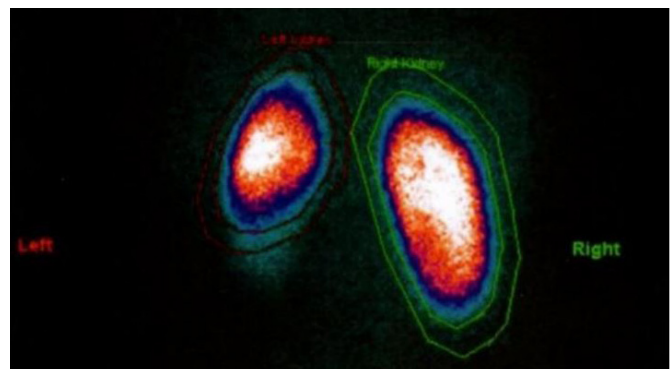


Figure 2. Static Renal Scintigraphy (DMSA) showing right kidney with 68% of its tubular function and left kidney with 32% with reduced volume and scar in the lower pole.

COMMENTS

Ring chromosome is usually caused by spontaneous and random errors during embryological development. It originates from terminal breaks in both the distal p and q arms, followed by fusion. Although it is a rare chromosomal abnormality, it may involve telomere pairing or deletion. The size of the deleted distal q arm (region 22q13) of chromosome 22 affects the overall phenotype. In this process, there may be deletion or interruption of the SHANK3 gene, which is found at the terminal end of chromosome 22q. In the case presented, it is not known whether the patient has SHANK3, as the study of her genetic alteration was not carried out with a molecular genetic test but with karyotype analysis, the most financially accessible test at that time^{4,5}.

The association of Phelan-McDermid syndrome (PMS) with congenital malformations is directly related to the size of the gene deletion. It promotes physiognomic, gastrointestinal, dental, ophthalmological, neurological and urological repercussions^{4,6,7}. Among the changes, the urological ones require a minimum deletion for their manifestation⁸.

In 2013, Soorya et al⁹ carried out a study with 30 autistic children and found an incidence of urological changes resulting from PMS in 38% of the sample, the main ones being vesico-ureteral reflux and hydronephrosis. In another study from 2014, Sarasua¹⁰ et al showed that 14% of the 201 PMS patients studied had vesico-ureteral reflux.

VUR has two treatment options: clinical and surgical. In general, patients with VUR are managed with drug therapy, which may include prophylaxis with antibiotics. Surgical treatment aims to prevent progression to chronic kidney disease and ends up being reserved for cases of persistent UTI, development of kidney scars or for patients who develop worsening kidney function¹¹. The patient in the case report was treated conservatively for two years with the use of anticholinergics and alpha blockers. However, there was a worsening of the loss of the renal parenchyma assessed by DMSA scintigraphy, indicating surgical intervention. The objective of surgery, however, is not the recovery of lost parenchyma, but the prevention of new lesions in an already diseased kidney.

Open surgeries to correct VUR have a success rate of 95-99% of cases¹². We opted for the Politano-Leadbetter intravesical technique, which consists of creating a submucosal tunnel in the direction of the medial bladder triangle to the original meatus to reestablish a competent valve system and interrupt urine reflux. It has a low rate of complications, with hematuria, ureteral stenosis and urine leakage being the most common, but none of them were observed in our patient's case¹³.

Finally, we can infer that although there are no established parameters to guide the evaluation and medical monitoring of PMS, the management of this pathology involves multidisciplinary care, assistance from complementary exams and routine outpatient follow-up to better outline each patient's therapeutic

plan. Follow-up of carriers must include complete history and physical examination since birth, including serial cognitive and behavioral assessments with the aim of ruling out other pathologies that present similar manifestations. The case reported in this paper exemplifies how each stage of this process is fundamental, and that clinical and surgical treatments must be combined in the individual management of patients with VUR, enabling the maintenance of their quality of life and functionality.

REFERENCES

1. Conte ML, Bertoli-Avella AM, de Graaf BM, Punzo F, Lama G, La Manna A, et al. A genome search for primary vesicoureteral reflux shows further evidence for genetic heterogeneity. *Pediatric Nephrology*. 2008 Apr;23(4):587-95
2. Quadros SA, Correa MB, et al. Refluxo Vesicoureteral em Crianças: atualização. *Arq Cat Med*. 2002;31(1):37-43
3. Denes FT, Arap S. Refluxo vésico-ureteral na infância. *J Pediatr (Rio J)* 1995;71:183-8
4. Phelan K, Rogers RC, Boccuto L. Phelan-McDermid Syndrome [Internet]. Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJ, Mirzaa G, et al., editors. PubMed. Seattle (WA): University of Washington, Seattle; 1993[cited 2022 Jun 1]. Available from: <https://pubmed.ncbi.nlm.nih.gov/20301377/>
5. Phelan K, Betancur C. Clinical utility gene card for: Deletion 22q13 syndrome. *Eur J Hum Genet*. 2010 Dec 8;19(4):492-2.
6. Kurtas N, Arrigoni F, Errichiello E, Zucca C, Maghini C, D'Angelo MG, et al. Chromothripsis and ring chromosome 22: a paradigm of genomic complexity in the Phelan-McDermid syndrome (22q13 deletion syndrome). *J Med Gen*. 2018 Jan 29;55(4):269-77.
7. Kolevzon A, Angarita B, Bush L, Wang AT, Frank Y, Yang A, et al. Phelan-McDermid syndrome: a review of the literature and practice parameters for medical assessment and monitoring. *J Neurodevelop Dis* [Internet]. 2014[cited 2022 Jun 1];6(1):39. Available from: <https://pubmed.ncbi.nlm.nih.gov/25784960/>
8. Samogy-Costa CI, Varella-Branco E, Monfardini F, Ferraz H, Fock RA, Barbosa RHA, et al. A Brazilian cohort of individuals with Phelan-McDermid syndrome: genotype-phenotype correlation and identification of an atypical case. *J Neurodevelop Dis* [Internet]. 2019 Jul 18[cited 2022 Jun 1];11(1):13. Available from: <https://pubmed.ncbi.nlm.nih.gov/31319798/>
9. Soorya L, Kolevzon A, Zweifach J, Lim T, Dobry Y, Schwartz L, et al. Prospective investigation of autism and genotype-phenotype correlations in 22q13 deletion syndrome and SHANK3 deficiency. *Mol Autism*. 2013;4(1):18.
10. Sarasua SM, Boccuto L, Sharp JL, Dwivedi A, Chen C-F, Rollins JD, et al. Clinical and genomic evaluation of 201 patients with Phelan-McDermid syndrome. *Hum Genet*. 2014 Jan 31;133(7):847-59.
11. Teixeira CBB, Cançado MA de P, Carvalhaes JT de A. Refluxo Vesicoureteral primário na infância: tratamento conservador versus intervenção cirúrgica. *Braz J Nephrol* [Internet]. 2014[cited 2022 Jun 1];36(1):10-7. Available from: <https://www.scielo.br/j/jbn/a/RyXhrHWYf446YfxsmZMDXSK/?lang=pt>
12. Miyakita H, Hayashi Y, Mitsui T, Okawada M, Kinoshita Y, Kimata T, et al. Guidelines for the medical management of pediatric vesicoureteral reflux. *Int J Urol: Official J Jap Urol Assoc* [Internet]. 2020 Apr 1[cited 2022 Jun 1]; Available from: <https://www.ncbi.nlm.nih.gov/pubmed/32239562>
13. Alberts VP, Idu MM, Legemate DA, Laguna Pes MP, Minnee RC. Ureterovesical anastomotic techniques for kidney transplantation: a systematic review and meta-analysis. *Transplant Int: Official J Eur Soc Organ Transplant* [Internet]. 2014 Jun 1 [cited 2022 Jun 1];27(6):593-605. Available from: <https://pubmed.ncbi.nlm.nih.gov/24606191/>