

A Tanzanian child with WAGR syndrome: A case report

Pius David Muzzazzi ^{1,*} and Kandi Catherine Muze ²

¹ Paediatric Haematology and Oncology fellow, Muhimbili University of Health and Allied Sciences, Paediatric Department, Dar es salaam, Tanzania.

² Paediatric Endocrinologist, Muhimbili National Hospital, Paediatric Department, Dar es salaam, Tanzania.

International Journal of Science and Research Archive, 2024, 12(02), 466–469

Publication history: Received on 28 May 2024; revised on 05 July 2024; accepted on 08 July 2024

Article DOI: <https://doi.org/10.30574/ijrsra.2024.12.2.1235>

Abstract

WAGR syndrome is a rare genetic disorder characterized by a de novo deletion of 11p 13 (PAX6 and WT1 genes), clinically associated with Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation. It affects 1 in 500,000 to 1 million people worldwide. Wilms tumor occurs in half of the children with WAGR syndrome. We admitted 3-year-old boy who presented in our institution with the complaints of delay in development milestones and abdomen distension. On thorough examination he was found to have aniridia, Wilms tumor, undescended testis and mental retardation. The observation that aniridia is associated with Wilms tumor led us to believe that the findings were consistent with WAGR syndrome. The diagnosis was confirmed by a genetic testing that revealed loss of 17840kb within the 11p15.1p12 chromosome, confirming the diagnosis of WAGR syndrome.

Keywords: Wilms tumor; aniridia; Genital urinary anomalies; Mental retardation; Genetic disorder

1. Introduction

WAGR syndrome is a rare genetic disorder characterized by a de novo deletion of 11p13 (PAX6 and WT1 genes) and is clinically associated with Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation (1). A combination of two or more of the mentioned clinical features is required for an individual to be diagnosed with WAGR syndrome.

WAGR syndrome affects 1 in 500,000 to 1 million people worldwide, affecting both males and females (2). In Tanzania, this condition is often overlooked during early childhood, and there is no documented data on the prevalence of this syndrome. However, most cases are diagnosed later in childhood when patients present with Wilms tumor. The unavailability of genetic testing further complicates the confirmation of diagnosis.

While aniridia is reported to be the most common presentation, Wilms tumor occurs in approximately half of the children with WAGR syndrome (3).

WAGR syndrome encompasses a wide range of genitourinary abnormalities, these include cryptorchidism, hypospadias, and renal and ureteral malformations. The spectrum of cognitive impairment varies significantly, spanning from typical cognitive function in some individuals to profound mental retardation in the majority (4).

Occasionally, WAGR syndrome may result from hereditary complexities involving genetic abnormalities in unaffected parents. Familiarity with WAGR syndrome and its clinical manifestations can offer crucial insights into the roles of the implicated genetic locus (5-6).

* Corresponding author: Pius David Muzzazzi

2. Case

We report on a 3-year-old boy referred from St. Benedict's Hospital in Ndanda, Mtwara, South Eastern Tanzania. He presented with a history of delayed developmental milestones since birth and progressive abdominal swelling for 8 months prior to admission.

The mother's pregnancy, child's birth history and family history were unremarkable. Neck control was attained at 8 months, started sitting and crawling at the age of 2 years and walked at the age of 3 years, but he was still unable to talk. He also has had aggressive behaviours, making it difficult to engage and play with his peers.

The abdominal distention was reported to be progressing gradually, more noticeable on the left side of the abdomen. He also experienced episodes of fevers and night sweats. There was no history of difficulty breathing or changes in bowel habits.

On admission, abdominal examination revealed asymmetrical distention, more pronounced on the left side with visible veins. A mass was palpable in the left hypochondriac and lumbar region, extending to the midline. It was non-tender, fixed, and had a smooth surface. Bowel sounds were present, and cryptorchidism was noted on examination of the genitalia. Ophthalmic examination revealed bilateral nystagmus and partially absent iris bilaterally (aniridia). Neurologically, the pupils were normal and equally reactive to light. In higher centers, he exhibited a blunt affect, prolonged fixation on objects, and inability to speak, although motor and sensory examinations were normal. The musculoskeletal exam revealed bilateral talipes equinovarus.

Routine blood investigations showed no abnormalities, while an abdominal ultrasound scan detected an echogenic mass measuring 48 x 44 x 52 mm in the inferior pole of the left kidney, a 12 mm lymph node in the left iliac region, and bilateral undescended testes located at the deep inguinal ring. Contrast-enhanced CT revealed a large lesion measuring approximately 56 x 58 mm with central areas of necrosis and surrounding solid areas involving the inferior and mid poles of the left kidney, with metastasis to the liver, but no lung metastasis was observed (figure 1). These findings led to the diagnosis of left Wilms' Tumor.

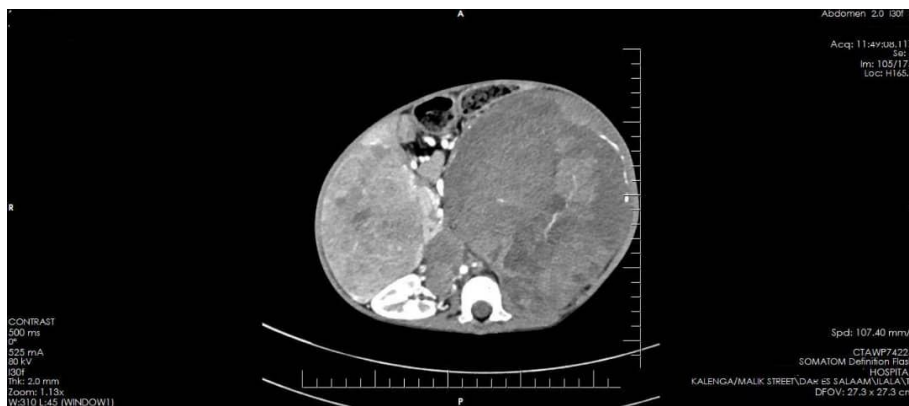


Figure 1 Contrast-enhanced CT revealed a large lesion measuring approximately 56 x 58 mm with central areas of necrosis and surrounding solid areas involving the inferior and mid poles of the left kidney

Genetic testing revealed a loss of 17,840 kb within the 11p15.1p12 chromosomal region (WT1 and PAX6 genes) identified by Next Generation Sequencing (NGS) Copy Number Variation (CNV) analysis and confirmed by Array Comparative Genomic Hybridization (aCGH), thereby confirming the diagnosis of WAGR Syndrome (figure 2).

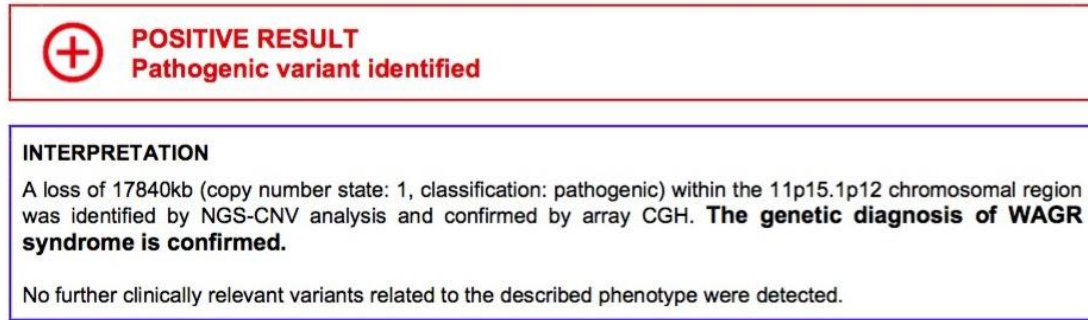


Figure 2 Genetic testing results confirmed the presence of WAGR syndrome

Ophthalmology review revealed reduced vision bilaterally, and he was planned for possible enucleation after chemotherapy. During his treatment for Wilms' tumor, a total of 10 weeks of adjuvant high-risk chemotherapy was administered. However, assessment at week 6 showed minimal shrinkage of the tumor and persistence of liver metastasis. Post-nephrectomy findings revealed residual tumor extending to the inferior vena cava (IVC) and involving the liver. Histology results confirmed nephroblastoma with diffuse anaplasia. The child underwent postoperative chemotherapy, completing a total of 31 weeks, and received whole-abdomen radiotherapy, resulting in complete resolution of the metastatic lesions as confirmed by a follow-up abdominal CT scan.

Regular oncologic follow-up is ongoing to date, and there have been no signs of relapse. His renal function tests remain normal. He also continues to receive ophthalmology and neurology follow-up care. The patient's parents have provided consent for the publication of the case details.

3. Discussion

Wilms tumor, aniridia, genital abnormalities, and mental retardation, described as WAGR syndrome, is a rare genetic disorder caused by a contiguous gene deletion involving the PAX6 and adjacent WT1 genes (1). The syndrome typically presents in the neonatal period with sporadic aniridia, and approximately one-third of neonates with sporadic aniridia will have WAGR syndrome. Therefore, it is crucial to screen all infants with sporadic aniridia for this syndrome. Aniridia is often followed by the development of Wilms' tumor in early childhood, though it can occur at any age (7).

Genetic testing using fluorescence in situ hybridization (FISH) is the preferred method to detect specific deletions (8). The treatment of WAGR syndrome is challenging and requires a multidisciplinary approach involving pediatric surgeons, ophthalmologists, neurologists, urologists, among others.

After confirming the diagnosis, it is important to perform abdominal ultrasound for Wilms' tumor screening. Patients with WAGR syndrome have an estimated 50% risk of developing Wilms tumor (3). For children without Wilms tumor, many institutions recommend a renal ultrasound every 3 months until the age of 6 years, then every 6 months until the age of 8, followed by annual screenings thereafter (5). However, follow-up should continue beyond these ages due to rare reports of late presentation of Wilms' tumor. Additionally, regular renal function tests are recommended, as there are reports of associated nephropathies with this syndrome (3). Neurological assessment is also crucial due to the wide spectrum of possible neurologic, behavioral, or psychiatric disorders associated with this syndrome (9-10).

In addition to aniridia, WAGR syndrome is associated with other ophthalmologic conditions such as cataracts and glaucoma. Therefore, a thorough ophthalmologic assessment is crucial for the treatment and ongoing monitoring of these conditions (11-12). In our case, the child exhibited clinical features indicative of WAGR syndrome early in infancy, which were subsequently confirmed through genetic testing. After confirmation, he underwent chemoradiotherapy and left nephrectomy, achieving complete remission. Presently, he receives regular multidisciplinary follow-up care.

4. Conclusion

In conclusion, this case study highlights the successful management of WAGR syndrome through early diagnosis, genetic confirmation, and comprehensive multidisciplinary treatment including chemoradiotherapy and nephrectomy. Regular follow-up has ensured sustained remission and ongoing monitoring of associated conditions. This study underscores the importance of prompt recognition and systematic management of rare genetic syndromes like WAGR, contributing

to improved outcomes and quality of life for affected individuals. Moving forward, continued research and awareness are essential to further enhance diagnosis, treatment strategies, and long-term care for patients with WAGR syndrome.

Compliance with ethical standards

Acknowledgement

The authors acknowledge Muhimbili National Hospital for granting ethical approval for this case report. We are grateful to the child's parents for consenting to the publication of this case for educational purposes. Furthermore, we appreciate the contributions of Dr. Lulu Chirande, Dr. Fathiya Said, and Dr. Sonal Patel in manuscript preparation.

Disclosure of conflict of interest

The authors declare no competing interests in this work. This manuscript received no funding from any financial or academic institution, and there are no conflicts of interest to disclose

Statement of ethical approval

Ethical clearance and approval were obtained from the Institutional Research Board of Muhimbili National Hospital

Statement of informed consent

Written informed consent was obtained from the parents, confidentiality was guaranteed, and administrative permission to publish this case report was granted by Muhimbili National Hospital as per hospital management protocols.

References

- [1] WAGR syndrome: a clinical review of 54 cases. Fischbach BV, Trout KL, Lewis J, Luis CA, Sika M. Fischbach BV, et al. *Pediatrics*. 2005 Oct;116(4):984-8. doi: 10.1542/peds.2004-0467. *Pediatrics*. 2005. PMID: 16199712
- [2] Meng Y, Yang J, Tian C, et al. Identification of a 6-month-old baby with a combination of WAGR and Potocki-Shaffer contiguous deletion syndromes by SNP array testing. *Hereditas*. 2020;157:23. doi:10.1186/s41065-020-00132-2
- [3] Duffy KA, Trout KL, Gunckle JM, Krantz SM, Morris J, Kalish JM. Results From the WAGR Syndrome Patient Registry: Characterization of WAGR Spectrum and Recommendations for Care Management. *Front Pediatr*. 2021 Dec 14;9:733018. doi: 10.3389/fped.2021.733018. PMID: 34970513; PMCID: PMC8712693.
- [4] Mahale A, Poornima V, Shrestha M. WAGR syndrome—a case report. *Nepal Med Coll J*. 2007 Jun 1;9(2):138-40.
- [5] Bernard V. Fischbach, MD; Kelly L. Trout, RN, BSN; Julia Lewis, MD; Catherine A. Luis; Mohammed Sika, PhD Reprint requests to (B.V.F.) Dallas Nephrology Associates, Division of Nephrology, Baylor University Medical Center, 3500 Gaston Ave, Dallas, TX 75246. E-mail: fischbachb@dneph.com, *Pediatrics* (2005) 116 (4): 984–988.
- [6] Moosajee M, Hingorani M, Moore AT. PAX6-Related Aniridia. In: *Gene Reviews*@[Internet]. University of Washington, Seattle; 2018
- [7] Tezcan B, Rich P, Bhide A. Prenatal Diagnosis of WAGR Syndrome. *Case Rep Obstet Gynecol*. 2015;2015:928585. doi: 10.1155/2015/928585. Epub 2015 Oct 28. PMID: 26605098; PMCID: PMC4641202
- [8] Crolla JA, Cawdery JE, Oley CA, et al. A FISH approach to defining the extent and possible clinical significance of deletions at the WAGR locus. *J Med Genet*. 1997;34:207-212
- [9] Jinno Y, Reeve A. Reply to “Parental origin of WT1 mutations and mental retardation in WAGR syndrome”. *Nat Genet*. 1994;8:13-14. <https://doi.org/10.1038/ng0994-13b>
- [10] Davis LK, Meyer KJ, Rudd DS, Librant AL, Epping EA, Sheffield VC, et al. Pax6 deletion results in aniridia, autism and mental retardation. *Hum Genet* 2008;123;371-8.
- [11] Lee H, Khan R, O'Keefe M. Aniridia: current pathology and management. *Acta Ophthalmol*. 2008 Nov; 86(7):708-15. doi: 10.1111/j.1755-3768.2008.01427.x. Epub 2008 Oct 6. PMID: 18937825.
- [12] Wang Q, Zhang X, Qin T, Wang D, Lin X, Zhu Y, et al. Unusual presentation in WAGR syndrome: expanding the phenotypic and genotypic spectrum of the disease. *Genes*. 2022;13(8):1431. <https://doi.org/10.3390/genes13081431>