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Case Report

Sequences of COVID-19 in a child with WAGR syndrome: A case report

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ABSTRACT

Introduction: and importance: WAGR syndrome is a rare genetic disorder consist of Wilms tumor, Aniridia, Genitourinary abnormalities, and Intellectual disability. During the enduring COVID-19 pandemic, it has become extremely important to document the properties of SARS-CoV-2 and its interactions with other diseases. Herein, we present the first case of Syrian child with WAGR syndrome that has been affected by COVID-19.

Case presentation: a 17-month-old boy was diagnosed with WAGR syndrome. During the follow-up, he developed rhinorrhea, cough, and moderate dyspnea with no fever. Computed tomography scan was normal and polymerase chain reaction test was positive. The child started an oxygen therapy with broad-spectrum antibiotics based on laboratory findings. His vital signs and laboratory values improved gradually without any further complications.

Discussion: COVID-19 has a special interest regarding its course in children. Although the clinical presentation varies, the current data reveal a better prognosis in children.

Conclusion: SARS-CoV-2 infection may result in non-specific symptoms and normal CT scan findings in children with WAGR syndrome. The accurate diagnosis, effective isolation and monitoring of the child, and successful management can improve the prognosis and shorten the infection period.

Grantor

Sami Jomaa.

1. Introduction

In December 2019, an outbreak of unexplained pneumonia emerged in China. Studies have exposed that it was first recorded in a local seafood market in Wuhan, China [1]. Later, the World Health Organization (WHO) stated the burst of a rapidly expanding pandemic termed coronavirus disease (COVID-19) caused by a novel virus named the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) [2].

The limited data about its impact on children, especially those with underlying diseases, has raised concerns [3]. Studies have revealed that children have a more desirable SARS-CoV-2 infection pattern and a better prognosis than adults [4–6]. However, a rigorous course of COVID-19 may develop in children with underlying chronic diseases such as immune deficiencies, malignancies, and asthma due to the continued systemic inflammation [6]. Moreover, the literature reported variant outcomes of children who were infected with SARS-CoV-2 and had a previous underlying disease, including congenital heart disease, prematurity, hydronephrosis, Down syndrome, and 18q deletion syndrome [3].

To provide more data about COVID-19 and whether it is associated with a more severe course in children with relatively rare diseases or not, we present the first case of a child with WAGR syndrome who was infected with SARS-CoV-2 during the period he was being prepared for the surgery and adjuvant chemotherapy.

This case report has been reported in line with the SCARE 2020 criteria [7].

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2. Presentation of case

A 17-month-old male is brought to our department due to abdominal distension for the last three months. His parents said that "he failed to gain weight gain despite his normal appetite". The child was born at term without any pregnancy-related complications. His weight at birth was 2.5 kg. He has been receiving his vaccines according to the National Vaccination Program. He looked very stiff, with tight muscles. He cannot walk nor respond to sounds around him. He cannot say a single word (e.g., mama or dada) or gain new ones. He shows no affection for his parents. He does not point to show things to others and does not copy others. His medical, surgical, and familial history was unremarkable. The parents mentioned being third-degree blood relatives. On admission, the child's weight and height were 7.3 kg and 70 cm, respectively. He was afebrile and had no signs of fatigue. He had a mild pallor with no history of vomiting or diarrhea. His blood pressure was 140/80 mmHg. A complete absence of bilateral iris with severe horizontal nystagmus and medial strabismus in the right eye was observed (Fig. 1). Fundal microscopy revealed typical findings without any abnormalities.

Clinical examination revealed a firm mass in the upper right quadrant, a right inguinal hernia, a subcoronal hypospadias, a small penis circumcised, and an absent right testicle (Fig. 4). No lymphadenopathy was determined. We also detected a right-sided flat foot (Fig. 2) with overlapped toes (Fig. 3). Laboratory tests revealed mild microcytic anemia (RBCs: 5.03 $\times$ 10^6/μl; Hemoglobin: 10.3 g/dl; MCV: 69 fl), a decreased platelet count (175 $\times$ 10^3/μl), a normal WBC count (11000 $\times$ 10^3/μl; Neutrophils: 49%; Lymphocytes: 44%), and normal kidney functional tests (creatinine: 0.4 mg/dL, urea: 18 mg/dL). Lab results also revealed elevated levels of FHS (0.41 mIU/ml: normal up to 0.20 mIU/ml) and decreased 17-hydroxyprogesterone levels (0.356 ng/ml: normal 0.50–2.4 ng/ml). LH and testosterone levels were within the reference range, 0.518 mIU/ml and 13.60 ng/dL, respectively. Pelvic ultrasound showed a mass measures 9.9 $\times$ 7.5 cm with clear borders and regular edges embracing most of the right kidney, pushing the inferior surface of the liver superiorly, and comply with Wilms tumor. A right migratory testicle in the right inguinal canal measuring 0.45 $\times$ 1.95 cm was observed. A normal shaped and positioned right kidney without hydronephrosis, calcifications, or stones was observed. Furthermore, a right inguinal hernia was detected. Computed tomography (CT) scan revealed a mass on the right kidney measures 9.9 $\times$ 7.5 cm (Fig. 5), with no other lesions.

We established our diagnosis with WAGR syndrome based on the clinical findings (Wilms tumor; Aniridia; Genitourinary anomalies; Mental Retardation) rather than the genetic testing; it was unavailable in our hospital, and the child parents cannot afford its expensive cost in a private center. However, aniridia and one or more other anomalies can confirm the diagnosis if genetic confirmation was unavailable.

During his follow-up and tuition for surgery, the child developed rhinorrhea, cough, and moderate dyspnea with substernal and subcostal retractions. The child was afebrile with no signs of cyanosis. Lung auscultation exposed fine bilateral crackles. A new chest CT scan was obtained, and the findings were unremarkable (Fig. 6). Based on the clinical features, we isolated the child, initiated oxygen therapy, and took a nasal swab to test for SARA-CoV-2 infection, which reported a positive result. Laboratory examinations at the isolation ward revealed elevated white blood cells (WBC) (16.4 $\times$ 10^3/μl; Neutrophils: 60%; Lymphocytes: 31%), platelets (484 $\times$ 10^3/μl), C-reactive protein (CRP) (9.66 mg/dL), fibrinogen (978 mg/dL), and D-dimer levels (203 ng/ml), with mild anemia (RBC: 4.40 $\times$ 10^6/μl; Hemoglobin 9.7 g/dl; MCV: 69 fl). His room-air oxygen saturation ranged between 84 and 86% and increased to 96–97% with an oxygen face mask. Due to the high

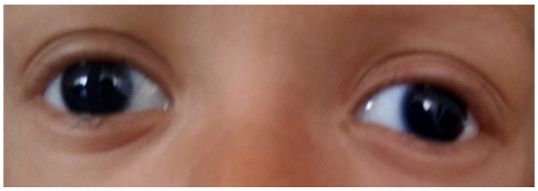

Fig. 1. Shows a complete bilateral absence of iris.

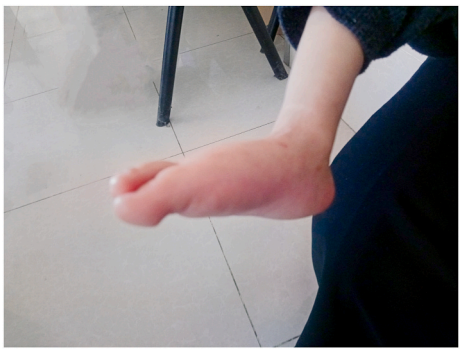

Fig. 2. Shows a right-sided flat foot.

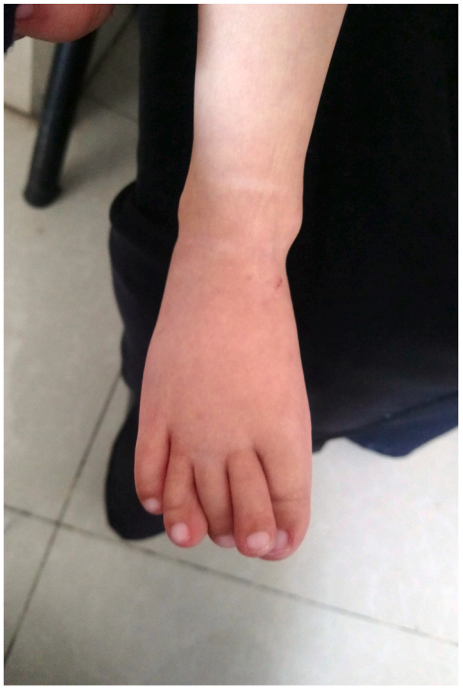

Fig. 3. Exposes a right-sided overlapped toes.

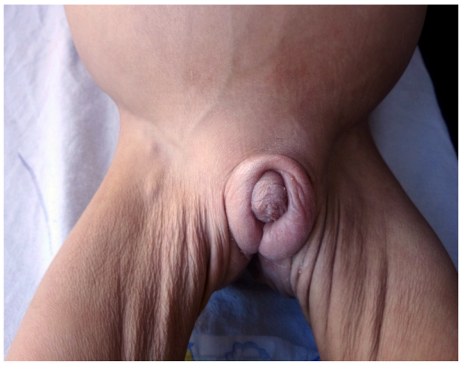

Fig. 4. Shows a small penis and an absent right testicle.

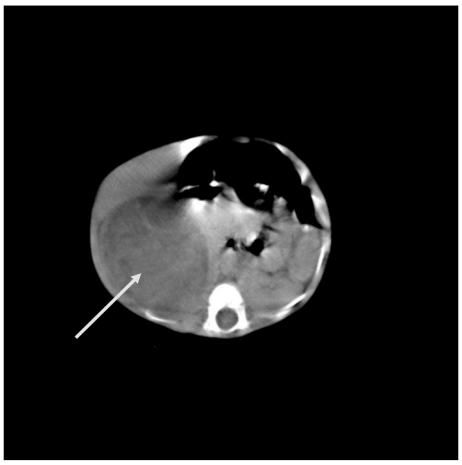

Fig. 5. Exhibits a mass on the right kidney measures 9.9 × 7.5 cm.

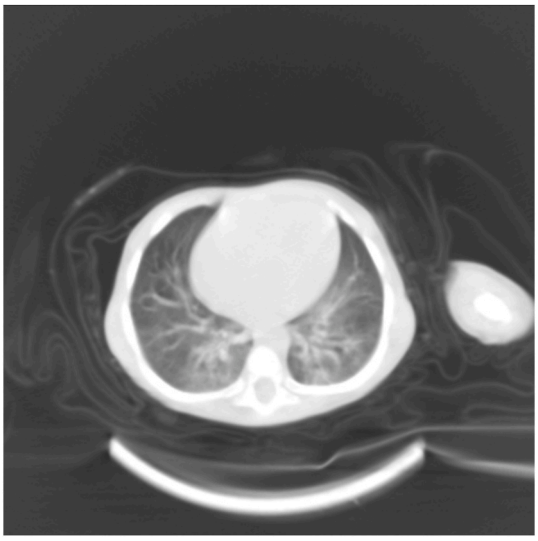

Fig. 6. Reveals a normal CT scan in a positive SARS-CoV-2 child.

procalcitonin levels (0.32 ng/ml) – which suggest a superimposed infection – we initiated therapy with broad-spectrum antibiotics, Vancomycin and Ceftriaxone; prednisolone was given as needed.

During the isolation, the child was in hemodynamic stability and has experienced neither a cardiovascular collapse nor thromboembolic events. His lungs auscultation, laboratory values, and oxygen saturation were improving gradually. Eight days after the isolation, his symptoms receded, lungs were clear to auscultation, CRP (0.4 mg/dL), Procalcitonin (0.14 ng/ml), D-dimer (136 ng/dL), Fibrinogen (246 mg/dL), and platelets (380 × 10^3/μl) levels return to normal levels, WBC count declined (11.7 × 10^3/μl; Neutrophils: 52.9%; Lymphocytes: 38.3%), anemia was improved (RBC: 5.20 × 10^3/μl; Hb: 12 g/dl; MCV: 73.4 fl), and oxygen saturation levels were stable. Based on the clinical and laboratory findings, we discharged the child and asked his parents to continue a 14-day quarantine at home. It is worth noting that the child was infected with coronavirus early in 2021, before the emergent of the Delta variant.

After two weeks, his parents brought him to resume his treatment plan. He appeared to be in a stable condition, with regular vital signs. He received neoadjuvant chemotherapy for four weeks – then underwent a laparotomy under general anesthesia. We observed a large mass at the expense of the right kidney and spread outside the kidney into nearby tissue. We performed a right nephrectomy with periaortic lymph node dissection while preserving the right adrenal gland. Gross examination of the excised mass revealed a necrotic mass measuring 14 × 10 × 9 cm. Histologic exam (Fig. 7) demonstrated a neoplastic proliferation consisting of three components, blastemal, epithelial, and stromal elements. The blastemal component is demarcated by the overgrowth of undifferentiated small to intermediate-sized cells with relatively small regular nuclei and small nucleoli. The epithelium consists of well-differentiated glomerular-like structures and trivial, mature tubules. Finally, the stroma is defined by spindle cells with oval to spindle-shaped nuclei and bland nucleoli, in addition to areas of necrosis. No residual tumor is apparent at or beyond the margins of excision, which results in a stage 2b tumor according to the NWTS grading system which used in our hospital.

The child received adjuvant chemotherapy consists of actinomycin D and vincristine for 28 weeks to eliminate any possible remaining cancer cells. CT scan was conducted six months later and revealed no signs of tumor relapse or metastasis. The right kidney did not show cortical thinning or other abnormalities. The patient suffered from vomiting, diarrhea, and hair loss, with a mild decrease in total blood count elements due to the adverse effects of chemotherapy. Kidney function tests were unremarkable, and the child has not experienced oliguria or hematuria. That implies COVID-19 may have no impact on the conventional prognosis of the underlying disease. However, long-term follow-up of renal function is mandatory.

3. Discussion

Our case presents the first case of WAGR syndrome accompanied by SARS-CoV-2 infection. WAGR syndrome (Wilms tumor, aniridia, genitourinary abnormalities, and mental retardation) is a rare genetic disorder marked by a predisposition to several conditions, including malignancies, eye abnormalities, and intellectual disability [8]. WAGR syndrome presents in various clinical pictures based on genes involvement, BDNF, WT1, and PAX6 mutations [9].

Wilms tumor is the most common renal tumor in children accounts for 6% of all childhood malignancies. It manifests with an abdominal mass, fatigue, anorexia, and weight loss. It is usually managed by transabdominal radical nephrectomy followed by chemotherapy consisting of actinomycin D and vincristine [10,11]. Studies have revealed that patients with unilateral Wilms tumor are less likely to develop a contralateral renal failure. Nevertheless, hyperfiltration injury and subsequent microalbuminuria are relatively common [10].

Aniridia is a rare condition with incidence ranges between 1:47,000 and 1:100,000 [12]. Due to the pan ocular effects of deletion of the PAX6 gene, most individuals with WAGR syndrome will suffer from moderate to severe visual impairment secondary to aniridia such as cataracts, glaucoma, nystagmus, or strabismus [8].

Genitourinary anomalies are more frequent in males, cryptorchidism being the most common anomaly [13]. Hypospadias and inguinal hernia also have been reported [8]. Interestingly, the previous three abnormalities were found together in our case.

Furthermore, musculoskeletal deformities have also been reported in patients with WAGR syndrome and presented with hypertense Achilles, scoliosis, kyphosis, metatarsal adductus, and talipes [8]. To our knowledge, this is the first report of a child with WAGR syndrome presenting with unilateral, right-sided overlapping toes and a flat foot. Genetic confirmation embraces WT1 and PAX6 gene involvement [9], whereas the clinical picture requires aniridia and one or more of the other anomalies [8].

During the COVID-19 pandemic, cases have been reported about children with SARS-CoV-2 infection and genetic syndromes, including Down syndrome, 18q deletion syndrome, and several unspecified genetic syndromes [3]. To the best of our knowledge, this is the first case in which SARS-CoV-2 infects a child who was diagnosed with WAGR syndrome during his follow-up and preparing for the management period.

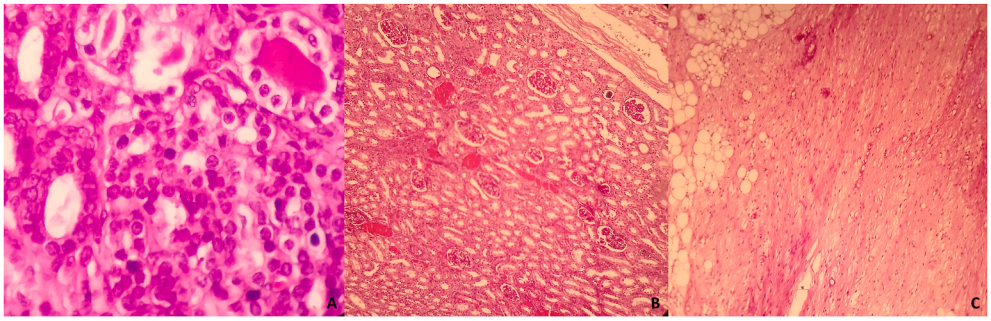

Fig. 7. A histologic images reveal the three components of Wilms' tumor. A: blastema consists of small to small-to medium-sized, round, blue, undifferentiated cells with relatively small regular nuclei and nucleoli cell. B: well-differentiated epithelial cells consist of glomerular-like structures and small, mature tubules. C: stromal cells showing no clear cell borders, oval to spindle-shaped nuclei with bland nucleoli. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Studies have shown that children have a more favorable prognosis compared to adults [4,5]. According to research data, children have an increased activity of the angiotensin-converting enzyme (ACE2); that may protect them against severe SARS-CoV-2 infection [6].

Since children often have frequent viral respiratory tract infections, it is possible that they were infected with one of the other common coronavirus strains when they have been recently vaccinated with live vaccines in their community, including Bacillus Calmette-Guerin, which can protect them from infection [6,14]. Because the immune system in children is not mature enough to trigger the cytokines storm, the symptoms tend to be less in severity [15]. Children tend to be less infectious as they have a lower viral load [6]. We believe that our patient got the virus from his community during the follow-up, as more than 95% of SARS-CoV-2 infections in infants had a community source [14].

Children exhibit a discrepancy in their presentation. Nonspecific symptoms of upper respiratory tract infection being the most frequent [6]. A systematic review of 38 studies reported that a total of 1117 infected children, 14.2% were asymptomatic, and about half of the patients experienced fever or cough [5]. Alternatively, rhinorrhea, nasal congestion, and respiratory distress are less frequent [5]. Another systematic review and meta-analysis of 65 studies have described the clinical symptoms of 1214 children; fever and upper respiratory symptoms were the most common, and their incidence rates were 38% and 35%, respectively [14]. According to a review, children's loss of scent is an uncommon symptom [5]. Although fever is the most common symptom, it can be within the normal range in some infected children as our patient. These findings suggest that COVID-19 symptoms are nonspecific and span from asymptomatic to extreme conditions.

Polymerase Chain Reaction (PCR) testing of the nasopharyngeal swab constitutes the gold standard diagnostic method for COVID-19 [15]. Furthermore, positive PCR children may reveal normal findings on CT scan [16].

While the decrease in WBC count is common [15], a systematic review of 174 cases has reported that it can be elevated, decreased, or within the normal range [5]. Tow systematic reviews have shown that CRP and procalcitonin levels were increased in 13.6% and 10.6% of cases [17], and 19.3% and 49.8% of cases, respectively [5]. Contrary, another review has reported that CRP and procalcitonin levels are usually normal [15].

A systematic review and meta-analysis of 1214 infected children reported that many children admitted to the hospitals had a mild progression of symptoms [14]. The primary reason for admission was for isolation commitments rather than consequences of the intensity of their medical situation [14]. Monitoring vital signs and providing oxygen through a high-flow nasal cannula, noninvasive ventilation, or ventilators are part of the management protocol [15,17]. A systematic review and meta-analysis have revealed that 22 of 354 patients received oxygen therapy, while only four required invasive ventilator support [14]. Blood tests and chest X-rays are necessary for follow-up [15,17]. Antibiotics can only be used for superimposed infections, not for empirical management. In severe cases, antiviral drugs are recommended [15,17].

To date, this is the first case report that describes the aligning of COVID-19 with a child diagnosed with WAGR syndrome. A unique systematic review has delineated the features of children with comorbidities and who were diagnosed with COVID-19 [3]. The outcomes have revealed that a small proportion of infected children with comorbidities face a higher risk of severe disease [3]. The most common comorbidities observed were chronic cardiac disease, diabetes mellitus, non-asthmatic chronic lung disease, asthma, and obesity [3].

4. Conclusion

COVID-19 still has concerns regarding its symptoms, prognosis, and outcomes in children, especially those with underlying chronic or rare diseases, such as WAGR syndrome. SARS-CoV-2 infection may result in non-specific symptoms (e.g., rhinorrhea, cough, and dyspnea) and normal CT scan findings in children with rare diseases. Moreover, the presence of fever is not predominant. However, the accurate diagnosis with PCR, effective isolation and monitoring of the child, and appropriate management can improve the prognosis and shorten the infection period.

Declarations

Conflicts of interest

The authors declared that they have no conflict of interest.

Ethical approval

Ethical approval was not required.

Sources of funding

No funding is required.

Author contribution

SJ obtained the information of this case. SJ, DS, MA, and IA drafted the manuscript. LK and SI revised the final draft. LK was the supervisor of this work. Registration of Research Studies: This is not an original research project involving human participants in an interventional or an observational study but a case report. This registration was not required.

Consent of patient

Written informed consent was obtained from the child's parents for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Provenance and peer review

Not commissioned, externally peer-reviewed.

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