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Case Report

A case report of an adolescent with ligase-4 deficiency and the potential dangers of ionizing radiation in this rare patient population ☆,☆☆

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ABSTRACT

DNA ligase IV deficiency is a rare disorder characterized by mutations in the LIG4 gene. Mutations in this gene cause a wide array of phenotypes, many of which are fatal early in life. We present an adolescent patient with heterozygous LIG4 mutations and the T-B-NK+ DNA ligase IV phenotype. Pelvic ultrasound and magnetic resonance imaging was completed to assess the patient's amenorrhea and delayed puberty, which demonstrated an atrophic cervix, distal vagina, and uterus without direct visualization of the ovaries. Early diagnosis of DNA ligase IV deficiency is important to minimize exposure to ionizing radiation from radiologic studies and preferentially utilize imaging studies that do not require ionizing radiation, such as ultrasonography and magnetic resonance imaging.

Introduction

DNA ligase IV deficiency (also known as Ligase IV syndrome) is a rare autosomal recessive disorder characterized by mutations in the LIG4 gene located on chromosome 13q33-q34. DNA ligase IV deficiency is accompanied with a wide range of phenotypes. Some clinical presentations include pancytopenia, microcephaly, primordial growth failure, developmental delay, marrow hypoplasia, growth retardation, unusual facial features, and predisposition to lymphoid malignancy [1,2]. Due to the rarity of disease and shortened lifespan, radiologic imaging findings are rarely reported in literature. In this case report, we present the imaging findings of a 16t-year-old female diagnosed with DNA ligase IV deficiency.

Case Presentation

The patient was born at 33 weeks gestation with placenta previa, intrauterine growth restriction (2 lbs 3 oz), and oligohy-

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dramnios necessitating induction of labor. At birth, the patient was admitted to the neonatal intensive care unit for her restricted growth, rectovaginal fistula requiring posterior sagittal anorectoplasty, and jaundice requiring phototherapy. When the patient was 2 years old, she was diagnosed with primordial dwarfism after presenting with microcephaly, small for gestational age, and global failure to thrive. Initially, these abnormalities were attributed to congenital cytomegalovirus infection due to a high viral load at birth, but no intracranial calcifications were found on prenatal ultrasound (US) of the brain. She was later diagnosed with DNA ligase IV deficiency by whole exome sequencing.

The patient was followed closely with pediatric hematology-oncology for chronic thrombocytopenia, often with platelet counts 20,000 to 40,000 per microliter (20-40 $\times$ 10^9 per liter). Despite consistently low white blood cell counts, the patient had never been hospitalized for infections. Her pancytopenia was macrocytic in nature, indicating bone marrow failure syndrome. She was found to have low IgG and IgA, and poor polysaccharide response and normal mitogen stimulation and complement function, consistent with the T-B-NK+ DNA ligase IV phenotype.

At 10 years of age, the patient had a human leukocyte antigen-matched sibling allogeneic bone marrow transplantation to treat progressively worsening thrombocytopenia and recurrent infections. Genetic analysis at that time revealed heterozygous LIG4 mutations (p.Y698X; p.R814X) and a de novo Xp22.31p22.32 duplication. At 15 years of age, the patient had Tanner 3 axillary and pubic hair, no body odor, absence of menarche, and no breast development (Tanner 1), secondary to hypergonadotropic hypogonadism likely due to DNA ligase IV deficiency and past chemotherapy. Laboratory testing revealed elevated FSH and low estradiol.

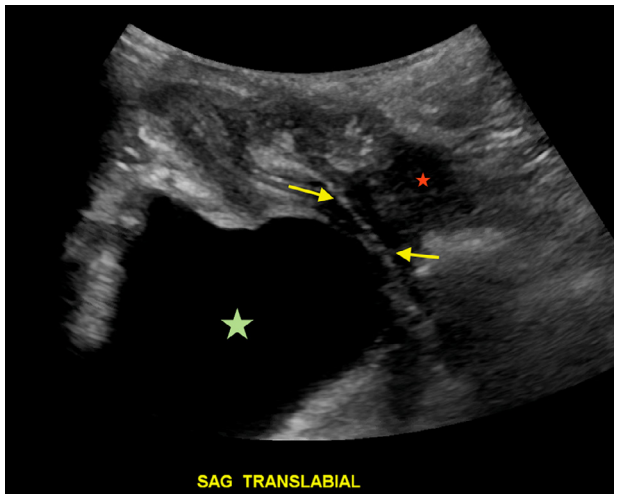

Fig. 1 – Translabial US of the pelvis in the sagittal planes demonstrating air (yellow arrows) within a tubular structure between the bladder (green star) and rectum (red star). (Color version of figure is available online.)

Due to the patient's delayed puberty secondary to ovarian failure, an US of the abdomen and pelvis (Fig. 1) was ordered. This did not demonstrate distinct uterine or ovarian tissue. Via the transperineal approach, air was seen within a tubular structure between the urethra and rectum. No free fluid was

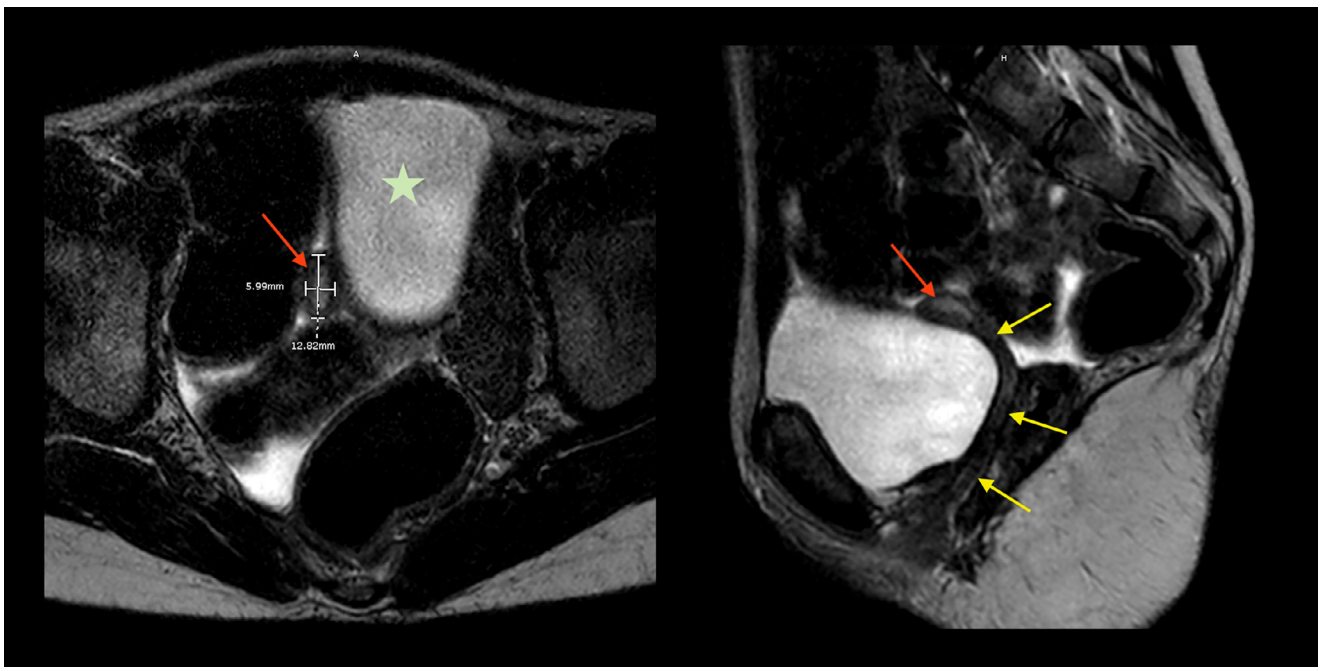

Fig. 2 – Small field-of-view T2-weighted axial and sagittal MR imaging of the pelvis without contrast demonstrating a tubular/ovoid-shaped structure (red arrow) adjacent to the urinary bladder (green star) which is continuous with a tubular structure containing fluid posterior to the bladder (yellow arrows). (Color version of figure is available online.)

identified in the pelvis. Follow-up magnetic resonance (MR) imaging of the pelvis without contrast (Fig. 2) demonstrated a tubular structure containing fluid posterior to the bladder, which likely represented a cervix and vagina. There was also a tubular and/or ovoid-shaped structure measuring approximately 1.3 × 0.6 × 0.6 cm (anteroposterior x transverse x craniocaudal) adjacent to the urinary bladder to the right, which appeared continuous with the tubular-appearing cervix. This structure likely represented an atrophic uterus. The ovaries were not appreciated within the adnexa.

To date, the patient is well-appearing with no recent history of severe infection, primary or secondary malignancy, or recurring bone marrow failure. The patient is on estrogen patches for her ovarian insufficiency.

Discussion

In 2019, a case review series by Boone *et al.* cited 41 published cases of DNA ligase IV deficiency, which revealed a female predominance (68%). The majority of cited patients had microcephaly (80%), growth failure (70%), infection (68%), hypogammaglobulinemia (83%), very low CD19+ B-cells (80%), and radiosensitivity (86%). Patients with bone marrow failure typically had signs and symptoms of pancytopenia or isolated thrombocytopenia or leukopenia. Other less common symptoms included dysmorphic facial features (37%), syndactyly/polysyndactyly (10%), congenital hip dysplasia (10%), skin involvement (20%), malignancy (24%), and bone marrow failure (44%) [3].

Several studies report incidences of pubertal delays and other reproductive disorders in the setting of DNA ligase IV deficiency. A case from 2018 described a patient who initially had three menstrual cycles but later developed amenorrhea. As with our case, MR imaging of the pelvis in this patient revealed a hypoplastic uterus and poorly visualized ovaries [4]. Two published cases describe female patients with elevated FSH and LH and low estradiol, consistent with hypergonadotrophic hypogonadism [4,5]. Another study described a male patient with DNA ligase IV deficiency with similar symptoms of male-related hypergondatrophic hypogonadism. This patient had a micropenis with a non-palpable left testis in which autopsy revealed the patient's left testis was marked with seminiferous atrophy [6].

Ionizing radiation may lead to DNA double strand breaks (DSB) through two mechanisms. The primary means involves high-energy radiation causing a release of electrons. These elections generate ions, which in turn, break the covalent bonds found in DNA [7]. The secondary cause of radiation-related DSBs involves direct DNA damage from reactive oxygen species [7,8]. Specifically, the reactive oxygen species generate apurinic and apyrimidinic sites within DNA, which induces strand breaks [7,8]. Non-homologous end joining (NHEJ), which uses DNA ligase IV, aids in repairing DSBs. The process of NHEJ involves at least five major repair complexes, including the XRCC4/ligase IV complex which is responsible for the final ligation step in NHEJ to ensure the two repaired strands join [3,8]. DNA ligase IV also plays a crucial role in V(D)J recombination and neural development [3,8,9].

Given the rarity of DNA ligase IV deficiency and its wide variety of phenotypes, is it important to differentiate it from Fanconi anemia, Seckel syndrome, and Nijmegen breakage syndrome, especially since the clinical presentations, such as microcephaly, facial dysmorphisms, and immune deficiency, are often shared [1]. These conditions all contain some degree of radiosensitivity and have an increased risk for malignancy and immunodeficiency. In a case series from 2019, all published cases of DNA ligase IV deficiency had radiosensitivity as seen by extensive damage to cell cultures when exposed to ionizing gamma radiation, although not all of the cases had microcephaly [3]. This finding is concerning since patients without the hallmark of microcephaly may still be radiosensitive if their DNA ligase IV deficiency remains undiagnosed.

As some patients may present with amenorrhea or signs and symptoms of hypergonadotropic hypogonadism, it is important to confirm the diagnosis in suspected cases prior to utilizing ionizing radiation (computed tomography, radiography, positron emission tomography, fluoroscopy, or mammography) to evaluate physical developmental delays. Following the diagnosis, radiologic studies using ionizing radiation should be kept to a minimum and, if required, methods to reduce the intensity and frequency of radiation should be utilized. Most diagnostic and surveillance imaging may be accomplished using MR imaging and US as they have high diagnostic ability and do not use ionizing radiation. US of the pelvis may be initially used to evaluate an etiology. In our patient, the atrophic cervix and distal vagina, seen as a tubular structure containing fluid posterior to the bladder, was visualized on both US, as well as follow-up MR imaging. The US did not identify the atrophic uterus, but MR imaging revealed an atrophic uterus as described by a tubular and/or ovoid-shaped structure. In both modalities, the ovaries were not visualized.

Conclusion

DNA ligase IV deficiency is a rare disorder that exhibits a wide array of phenotypes. Due to the significant radiosensitivity, it is highly advised to avoid imaging studies that utilize ionizing radiation. Ultrasound and magnetic resonance imaging provide a safe and effective method to diagnosing and evaluating patients with DNA ligase IV deficiency. In patients with DNA ligase IV deficiency, ultrasound and magnetic resonance imaging of the pelvis may show an atrophic cervix, distal vagina, and uterus. The adnexa of the uterus and ovaries may be hypoplastic or atrophic.

Patient consent

No consent obtained for this case report as this is a retrospective study with no patient identifiers.

"Formal consents are not required for the use of entirely anonymized images from which the individual cannot be identified - for example, x-rays, ultrasound images, pathology slides or laparoscopic images, provided that these do not contain any identifying marks and are not accompanied by text that might identify the individual concerned."

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