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Immunological Complications and Treatment of Cryptorchidism in Children: A Surgical and Immunotherapeutic Perspective

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Abstract: Cryptorchidism, a common congenital urogenital abnormality affecting 1–5% of full-term male infants, involves the failure of the testicles to descend into the scrotum. This study aimed to evaluate the surgical outcomes in children with cryptorchidism and the effectiveness of rituximab-based immunotherapy for associated paraneoplastic autoimmune encephalitis. This study assessed the surgical outcomes of 1,290 children aged 8 months to 15 years who were treated for cryptorchidism at two facilities in Bishkek, Kyrgyzstan, between 2021-2024. Patients underwent surgery based on testicular location, with 134 treated using the Torek method, 1,055 using the Sokolov method, and 101 using the Petrivalsky/Shoemaker methods. Of the patients who underwent surgery before the age of 3 years, 46.4% had better outcomes. The inguinal region was the most common testicular location (97.1%), with 2.9% of the cases involving abdominal testes. Postoperative ultrasound revealed complications in 62.9% of patients who underwent the Torek method. Three patients with anti-N-methyl-D-aspartate receptor encephalitis associated with germ cell tumors were treated with tumor resection, corticosteroids, plasmapheresis, and rituximab, resulting in neurological recovery in all cases. This study emphasizes the importance of early surgical intervention and multidisciplinary management of cryptorchidism and its associated complications.

Keywords: Cryptorchidism; Rituximab; Germ Cell Tumor; Anti-NMDAR Encephalitis; Pediatric Oncology; B Cell Depletion

1. Introduction

Cryptorchidism is one of the most common congenital urogenital abnormalities in male infants, affecting 1–5% of full-term babies and up to 30% of premature births [1, 2]. This condition involves the failure of one or both testicles to descend into the scrotum, which can lead to potential complications if left untreated. These include reduced fertility, hormonal disturbances, and an increased risk of testicular cancer [3, 4]. Early surgical correction, typically orchiopexy, is recommended between 6 and 18 months of age to optimize testicular function and reproductive potential [2, 3, 5]. Hormone therapy remains controversial because of its limited effectiveness and is not

recommended as a standalone treatment [2, 6].

Testicular descent during fetal development is controlled by hormones such as insulin-like peptide 3 and testosterone. Interruptions in these hormonal pathways, possibly due to genetic abnormalities or environmental influences, contribute to cryptorchidism [1, 3]. Key risk factors include low birth weight, premature birth, and genetic susceptibility, suggesting a multifaceted origin [1, 7].

Surgical orchidopexy aims to reposition the testes to reduce infertility and cancer risk [2, 5]. Early intervention is associated with better preservation of sperm production [8, 9]. Hormonal treatments using human chorionic gonadotropin or gonadotropin-releasing hormone have limited success and are recommended only as adjuncts to surgery in certain cases [6, 8].

Gonadal functional capacity after treatment is influenced by factors such as age at intervention, initial testicular position, and duration of the undescended state. Timely surgical correction is advised to maintain long-term reproductive and endocrine function, although some inconsistencies exist regarding its effects on hormone levels and testicular size in adulthood [9].

Various factors that influence incidence rates, such as genetic susceptibility, environmental influences, and access to healthcare, differ across regions [10, 11]. Epidemiological research has revealed diverse prevalence rates across Europe, highlighting geographical differences that may be linked to risk factors and inconsistencies in data collection and reporting [12, 13].

The incidence of cryptorchidism in Kyrgyzstan has not been well-documented. Based on global patterns, its prevalence is likely to align with the international average for full-term newborns. Region-specific data are vital for understanding the local determinants of cryptorchidism, including socioeconomic factors and genetic preposition. This knowledge is crucial for tailoring healthcare strategies to address cryptorchidism and its implications, including fertility issues and the risk of testicular cancer [1, 3, 8]. Such research aligns with guidelines that advocate for early surgical intervention between 6 and18 months to reduce complications [2].

Cryptorchidism contributes to testicular germ cell tumors (TGCT), with 10% of cases occurring in males with cryptorchidism [14]. Surgical correction is performed before 18 months of age to reduce the risk of cancer. Cryptorchid TGCT may cause complications more common in ovarian GCTs, including torsion, rupture, and paraneoplastic disorders like anti-N-methyl-d-aspartate receptor autoimmune encephalitis (anti-NMDAR AE). Understanding the local disease burden and evaluating surgical efficacy are crucial for providing effective patient care. Given the reproductive implications of cryptorchidism, this study aimed to examine surgical outcomes and identify factors affecting fertility disorders.

This study evaluated various surgical methods for treating cryptorchidism in children, with a focus on preserving testicular function and maintaining future fertility potential. This study examined the immunological issues associated with TGCT, particularly anti-NMDAR AE, and investigated the effectiveness of rituximab-based immunotherapy in promoting neurological recovery and long-term remission in pediatric patients.

2. Methods

This cross-sectional study was conducted at the City Children's Clinical Hospital of Emergency Medical Aid and the National Center for Maternity and Childhood Welfare in Bishkek, Kyrgyzstan, from 2021 to 2024. This study included 1,290 children aged 8 months to 15 years who sought treatment for cryptorchidism. All patients underwent surgical procedures to reposition the testicles into the scrotum. Patients were categorized based on the surgical approach used: 134 underwent the Torek method, 1,055 the Sokolov method, and 101 the Petrivalsky/Shoemaker method. The control group included 32 healthy children without genitourinary issues. The mean age of the participants was 4.8 years (range, 1–15 years).

The assessment protocol included standard laboratory tests, ultrasound examinations of internal organs and the scrotum using Doppler ultrasound (DUS), and measurements of testicular size before and after surgery. Computed tomography (CT) and magnetic resonance imaging (MRI) were used for testicular localization and positioning evaluation when necessary. Hormonal assessments included testosterone, follicle-stimulating hormone, luteinizing hormone, and prolactin levels. Excretory urography was performed to assess the potential urinary tract abnormalities.

Some patients with cryptorchidism and neurological symptoms underwent immunological assessments, including serum tests for anti-NMDAR antibodies, to confirm AE. Other immunological factors were not routinely

evaluated.

The surgical techniques varied according to the testicular location and anatomical factors. The Torek method involves separating the testicle from the vaginal peritoneum and relocating it to a prepared scrotum. In some cases, the testis was sutured to the thigh fascia to enhance stability. The Sokolov method involves additional suturing of the inner thigh skin to reduce tension on the spermatic cord. The Petrivalsky/Shoemaker method involves fixing the testicle to the scrotal dartos fascia to optimize its mobility. Laparoscopic procedures were performed on the intra-abdominal testicles. Orchiectomy was performed for significantly hypoplastic testicles, followed by histological analysis of excised tissues.

Postoperative monitoring included US evaluations at 1, 6, and 12 months to assess the testicular position, vascularization, and volume preservation. The testicular volume was calculated using the following formula: V = length × width × height × 0.52. The mean blood flow velocity in the testicular artery was measured using DUS. Surgical success was evaluated based on postoperative complications, testicular atrophy, and cryptorchidism recurrence. Hormonal therapy was considered for patients with persistent gonadal dysfunction after consultation with an endocrinologist.

An immunotherapy treatment plan was implemented for anti-NMDAR encephalitis associated with TGCT. Rituximab, a monoclonal antibody targeting CD20, was administered intravenously at 375 mg/m^2 weekly for four weeks, following the protocols for AE and B-cell lymphoproliferative disorders. The reasons for using rituximab included reducing B cells to lower autoantibody production contributing to encephalitis, improving the effectiveness of corticosteroids and plasmapheresis, and preventing relapse by maintaining immunomodulation after tumor removal. This strategy was combined with high-dose corticosteroids and, in certain cases, with intravenous immunoglobulin or plasmapheresis. Treatment effectiveness was tracked using serial magnetic resonance imaging (MRI), positron emission tomography/computed tomography (PET/CT) scans, and clinical neurological evaluation.

Descriptive and inferential statistics were used to evaluate testicular volume, mean blood flow velocity, and hormone levels among the surgical groups. This study adhered to ethical standards, with informed consent obtained from parents or guardians prior to participation. This study was conducted in accordance with the Declaration of Helsinki (2013) and received approval from the Bioethical Committee of I.K. Akhunbaev Kyrgyz State Medical Academy (Protocol No. 9, dated January 22, 2022).

3. Results

The prevalence of children with abnormally positioned testicles in specialized facilities is increasing, although cases among children over 3 years of age are decreasing, likely due to enhanced local education. Delayed treatment contributes to impaired sperm production in undescended testicles, starting as early as the second year of life. For children undergoing surgery after 7 years of age, fertility potential decreases to 25%. Among the studied cases, 707 (54.8%) boys had a missing testicle in the right scrotum, 546 (42.3%) in the left scrotum, and 37 (2.9%) had bilateral cryptorchidism.

Associated congenital abnormalities were identified in 25 patients with impaired testicular descent, including hydronephrotic transformation in 2 (0.2%), incomplete kidney duplication in 15 (1.2%), pyelectasis in 35 (2.7%), hypospadias in 2 (0.2%), anal opening narrowing and ectopia in 3 (0.2%), and inguinal hernias in 12 (0.9%) children. **Table 1** presents the distribution of children by age and testicular location.

Table 1. Distribution of children by age and location of the testicle in the observed patients.

Localization		Age				
		<1 year	**1–3 years**	**4–7 years**	**8–11 years**	**12–16 years**
One-sided	Inguinal	102 (7.9%)	447 (34.6%)	513 (39.8%)	110 (8.5%)	41 (3.2%)
	Abdominal	8 (0.6%)	12 (0.9%)	9 (0.7%)	1 (0.1%)	-
Double-sided	Inguinal	4 (0.3%)	13 (1.0%)	12 (0.9%)	1 (0.1%)	-
	Abdominal	-	3 (0.2%)	4 (0.3%)	-	-
Total		114 (8.8%)	485 (37.6%)	538 (41.7%)	112 (8.7%)	41 (3.2%)

Note: Values are presented as the n (%).

As shown in **Table 1**, 599 (46.4%) patients underwent surgery before the age of 3 years, whereas 691 (53.6%) were treated later. The testicle was most commonly found in the inguinal region, accounting for 1253 (97.1%) cases, whereas the abdominal testicle was observed in 37 (2.9%) children. The latter requires additional diagnostic procedures, including abdominal DUS, CT, and MRI. Of the 37 abdominal cases, 24 (64.9%) were diagnosed using DUS, and 13 (35.1%) were identified laparoscopically. Although numerous surgical techniques exist for descending the testicle into the scrotum, this study used the methods outlined in **Table 2**.

Table 2. Year-wise distribution of orchiopexy methods used in pediatric cryptorchidism (2021–2024).

Methods	2021	2022	2023	2024	Total
Torek	22 (14.1%)	31 (13.0%)	44 (9.4%)	37 (8.6%)	134 (10.4%)
Sokolov	134 (85.9%)	182 (76.5%)	377 (80.7%)	340 (79.3%)	1055 (81.8%)
Petrivalsky/Shoemaker	-	18 (7.5%)	39 (8.5%)	44 (10.3%)	101 (7.8%)
Laparoscopic	-	4 (1.7%)	5 (1.1%)	4 (0.9%)	13 (1.0%)
Orchiectomy	-	3 (1.3%)	6 (1.3%)	4 (0.9%)	13 (1.0%)

Note: Values are presented as the n (%).

Table 2 shows the significant decrease in the use of the Torek method for orchiopexy. This decline is related to improved testicular descent procedures, the need for staged treatments, and extended medical and social adaptation for patients. Of the 37 patients with abdominally located testes, single-stage descent into the scrotum was achieved in 32 (86.5%). The remaining five (13.5%) patients underwent two-stage lowering because of short spermatic cords and blood supply concerns. Laparoscopic diagnosis and treatment were performed in 13 patients. Severe gonadal atrophy was not observed, despite the abdominal positioning.

Testicular descent uses established techniques for each method of intervention. The main approach involved separating the testicle from the vaginal peritoneum and relocating it to a prepared area at the base of the scrotum for its fixation. To prevent recurrence, some cases involved suturing the testicle to the thigh fascia and creating a Torek anastomosis. This improved fixation induces spermatic cord tension, potentially disrupting the blood supply and causing aseptic gonadal inflammation. The Sokolov method involved additional suturing of the inner thigh skin, while the Petrivalsky/Shoemaker method fixed the testicle to the scrotal dartos fascia, both aiming to reduce the cord tension and enhance mobility.

Prior studies on children with bilateral abdominal and inguinal testicular retention assessed hormonal status and gonadal volume before the surgery. These results revealed a directly proportional relationship in bilateral cases, whereas unilateral cases showed changes only in gonadal volume. Blood plasma testosterone levels were normal in most children. Orchiectomy was performed on severely hypoplastic testicles (less than 4 mm in size). Histological examination of the excised gonads revealed total testicular sclerosis in all 13 cases.

Table 3 shows that during scrotal sonography, the average volume of the descended testicle was 0.91 ± 0.9 cm3, with the abdominal form testicle being larger than that in inguinal retention cases. After the Torek method, DUS revealed changes in 51 (62.9%) children, including testicular or epididymal alterations, membrane fibrosis, parenchymal compaction, hyperechoic tubular inclusions, sclerotic changes, and reduced testicular volumes. DUS measurements showed average testicular artery blood flow velocities in the operated testicle of 8.2 ± 1.3 cm/s for the first group and 11.2 ± 0.8 cm/s for the second group, compared to 12.8 ± 0.2 cm/s and 12.2 ± 0.6 cm/s on the healthy side, respectively.

In the 15 patients in the second group with abdominal testicular retention, the Doppler frequency spectrum and qualitative indicators of testicular blood flow showed minimal changes. Hormonal therapy was administered in addition to surgery when significant decreases in gonadotropin levels and gonadal volume indicators were observed.

Table 3. Year-wise distribution of orchiopexy methods used in pediatric cryptorchidism (2021–2024).

Methods	Gonadal Condition							
	Unilateral Inguinal Retention (n = 26)		Bilateral Inguinal Retention (n = 22)		Unilateral Abdominal Retention (n = 21)		Unilateral Abdominal Retention (n = 12)	
	Mean Age - 3.2 years		Mean Age - 2.8 years		Mean Age - 3.7 years		Mean Age - 2.8 years	
	MTV, cm^3	DUS of Testicular Vessels	MTV, cm^3	DUS of Testicular Vessels	MTV, cm^3	DUS of Testicular Vessels	MTV, cm^3	DUS of Testicular Vessels
		MBFV, cm/s		MBFV, cm/s		MBFV, cm/s		MBFV, cm/s
Torek	0.89 ± 1.5	8.4 ± 0.5	0.87 ± 1.2	8.1 ± 0.9	0.96 ± 0.7	8.7 ± 1.2	0.93 ± 0.5	8.3 ± 0.02
Sokolov		9.9 ± 0.9		10.4 ± 0.6		11.6 ± 0.6		9.2 ± 0.45
Petrivalsky/ Shoemaker		11.1 ± 0.3		10.9 ± 1.2		11.9 ± 0.4		10.3 ± 0.9

Note: Values are expressed as the mean±standard deviation. MTV: Mean testicular volume; DUS: Doppler ultrasound; MBFV: Mean blood flow velocity.

3.1. Immunological Case Analysis

A 15-year-old male was admitted to the ICU with recurring seizures, convulsions, and a GCS score of 7/15. He presented with fever, rapid breathing, and an elevated heart rate, which required intubation. A CT scan revealed a pelvic mass extending into the left inguinal canal. Pelvic ultrasound revealed a heterogeneous mass, and scrotal ultrasound confirmed the presence of a single right testicle. Blood tests revealed elevated alpha-fetoprotein (45 ng/mL) and lactate dehydrogenase (486 U/L) levels, indicating left-sided cryptorchidism with TGCT involvement. Serum antibody tests confirmed the diagnosis of anti-NMDAR AE. Positron emission tomography (PET)/CT revealed increased radiotracer uptake in the pericallosal brain region, and MRI revealed edema in the cingulate gyrus and restricted diffusion in the occipital lobes. The patient's hemoglobin level dropped from 12.8 to 6.6 g/dL, and a follow-up CT showed an increase in the mass size and hemoperitoneum, suggesting tumor rupture. The mass was surgically excised, confirming a mixed GCT (60% mature teratomas and 40% seminomas) with adjacent tissues. Treatment included corticosteroids, plasmapheresis, and rituximab (375 mg/m^2) for encephalitis. Neurological improvement was observed within two weeks, and an MRI revealed the resolution of abnormalities after 20 days. The patient was started on chemotherapy with cisplatin, etoposide, and ifosfamide and was disease-free on follow-up CT 15 days after discharge (**Table 4**).

Table 4. Summary of clinical, laboratory, imaging, and therapeutic data for pediatric patients with anti-NMDAR AE and TGCT.

Patient	Tumor Type	Tumor Markers	Immunotherapy	Chemotherapy	Neurological Recovery	Follow-Up
15-year-old male	Mixed GCT (60% teratoma, 40% seminoma)	AFP - 45 ng/mL, LDH - 486 U/L	Rituximab (375 mg/m^2 x 4 weeks) + Corticosteroids + Plasmapheresis	Cisplatin, Etoposide, Ifosfamide	Improved within 2 weeks	Disease-free at 15 days, no recurrence.
12-year-old male	Seminoma	β-hCG - 160 mIU/mL	Rituximab (375 mg/m^2 x 4 weeks) + Corticosteroids + IVIG	-	Improved within 2 weeks	Complete recovery by 3 months.
14-year-old male	Mixed GCT (50% yolk sac tumor, 30% seminoma, 20% immature teratoma)	AFP - 58 ng/mL	Rituximab (375 mg/m^2 x 4 weeks) + Corticosteroids + Plasmapheresis	Cisplatin, Etoposide, Ifosfamide	Improved within 3 weeks	Full neurological recovery at 3 months.

Note: GCT: Germ cell tumors, AFP: Alpha-fetoprotein, LDH: Lactate dehydrogenase, β-Hcg: β-human chorionic gonadotropin, IVIG: Intravenous immunoglobulin.

The second case involved a 12-year-old boy who was admitted with confusion, aggressive behavior, and seizures. He had untreated left-sided cryptorchidism. Brain MRI revealed an increased T2 signal in the cingulate gyrus and thalamus, whereas PET/CT revealed heightened temporal lobe uptake and decreased occipital lobe uptake. Pelvic ultrasound revealed an intra-abdominal testis with a heterogeneous mass. Tumor markers showed elevated β-hCG levels of 160 mIU/mL. Laparoscopic orchiopexy was performed, and histological examination confirmed the diagnosis of seminoma. Serum tests confirmed the presence of anti-NMDAR antibodies. Treatment included corticosteroids, intravenous immunoglobulin, and rituximab (375 mg/m^2) weekly for four weeks. The patients demonstrated improvement during the first two weeks before achieving complete recovery by the third month (**Table 4**).

The third case involved a 14-year-old boy with a history of bilateral cryptorchidism who underwent orchiopexy for right-sided cryptorchidism at the age of five years. He presented with hallucinations, memory impairment, and behavioral changes. Brain MRI revealed increased signal intensity in the left temporal lobe and thalamus, whereas PET/CT scan revealed reduced activity in the occipital lobe. Pelvic MRI revealed a left testicular mass with hemorrhagic changes. Tumor markers showed elevated alpha-fetoprotein levels (58 ng/mL), and serum analysis confirmed the presence of anti-NMDAR antibodies. The left intra-abdominal testicle was removed laparoscopically, and histology revealed a mixed germ cell tumor (50% yolk sac tumor, 30% seminoma, and 20% immature teratoma). The patient was administered chemotherapy with cisplatin, etoposide, and ifosfamide. Immunotherapy consisted of rituximab (375 mg/m^2 administered weekly for four weeks), corticosteroids, and plasmapheresis. Neurological improvements were observed within three weeks, with follow-up imaging demonstrating the resolution of abnormalities on MRI and PET/CT scans. Cognitive and motor functions were restored within three months (**Table 4**).

3.2. Immunological Results and Responses to Immunotherapy

Three patients with cryptorchidism exhibited neurological symptoms of AE and were confirmed to have anti-NMDAR encephalitis. Serological tests confirmed the presence of anti-NMDAR antibodies in all patients, suggesting an autoimmune and paraneoplastic origin. Tumor markers were significantly elevated: in the first case, alpha-fetoprotein (AFP) was 45 ng/mL and lactate dehydrogenase (LDH) was 486 U/L; in the second case, β-human chorionic gonadotropin (β-hCG) was 160 mIU/mL; and in the third case, AFP was 58 ng/mL (Table 4). Neuroimaging showed increased radiotracer uptake in the pericallosal area on positron emission tomography/computed tomography, with edema and restricted diffusion in the cingulate gyrus and occipital lobes on brain MRI, supporting the diagnosis of autoimmune encephalitis.

All three patients underwent surgery to remove the TGCT, followed by immunotherapy. The treatment involved rituximab at 375 mg/m^2 weekly for four weeks. Each patient received high-dose corticosteroids and plasmapheresis, and one patient received intravenous immunoglobulin. Neurological improvements were observed within 14–21 days of initiating the immunotherapy. MRI and PET/CT scans revealed that the abnormalities had resolved 20–30 days post-treatment. Two patients fully regained cognitive and motor functions within three months, while one patient experienced early hematologic recovery, with CT scans confirming disease-free status 15 days after discharge.

Although quantitative post-treatment anti-NMDAR antibody measurements were unavailable, rapid clinical recovery and normalized imaging results suggest effective treatment. None of the three patients experienced recurrent neurological symptoms during the follow-up period. Rituximab was well tolerated, with no adverse events or infusion reactions. These results highlight the immunomodulatory benefits of rituximab in treating paraneoplastic anti-NMDAR encephalitis associated with testicular GCTs in pediatric patients.

4. Discussion

4.1. Surgical Outcomes and Implications

This study conducted a comparative analysis of the surgical outcomes of cryptorchidism in pediatric patients and explored the potential reproductive complications. Our results emphasize the importance of early surgical intervention, specifically orchiopexy, ideally performed between 6 and 12 months of age. Timing is crucial, as demonstrated by improved testicular outcomes and reduced fertility-related issues in children who receive early treatment. These findings align with the current guidelines from the European Association of Urology and the American Urological Association, which recommend prompt surgical intervention to improve future reproductive health outcomes [2, 5].

The testicle located outside the scrotum is initially damaged as a result of intrauterine injury [15]. Relapses after surgical lowering of the testicle into the scrotum by various methods were noted in 28 (2.2%) patients, including 11 (0.8%) according to the Sokolov method, 13 (1.0%) according to the Petrivalsky/Shoemaker method, and 4 (0.3%) according to the Torek method. In cryptorchidism surgery, the primary goal is not cosmetic (lowering the testicle into the scrotum at all costs), but reproductive (preservation of its function) [16, 17]. Surgical intervention in various forms of testicular retention is an indication for subsequent observation of the child by a urologist-andrologist for timely examination of the reproductive system and, if there is a violation, timely correc-

tion.

Examining the outcomes of surgical interventions for cryptorchidism in pediatric patients offers insights into the timing and techniques of orchiopexy. A significant proportion (46.4%) of procedures before the age of 3 adhered to guidelines advocating early intervention for testicular health and fertility. However, 53.6% of patients requiring additional surgery underscored challenges, such as late diagnosis or limited healthcare access, emphasizing the need for systemic improvements to enhance early treatment adherence.

4.2. Disruption of Testicular Immune Privilege

TGCT, particularly those associated with cryptorchidism, are highly immunogenic cancers with a unique tumor microenvironment rich in immune components. GCTs contain tumor-infiltrating lymphocytes, which show an active host immune response and exhibit PD-L1 on tumor or immune cells, enabling immune escape. This immunological environment may explain the connection between GCTs and paraneoplastic autoimmune syndromes, such as anti-NMDAR AE, in which antibodies target neuronal antigens after tumor exposure.

The high prevalence of undescended testes in the inguinal area (97.1%) aligns with common clinical patterns, whereas a small fraction (2.9%) involves abdominal testes, requiring advanced imaging, such as DUS and laparoscopy, for localization and surgical planning [1, 2]. The surgical trend shows a significant decrease in the use of the Torek method, driven by progress in alternative techniques yielding better results and fewer stages, with an 86.5% success rate for single-stage abdominal testicular descent [2, 6]. Two-stage treatment remains crucial for cases with anatomical limitations, such as short spermatic cords [18].

Laparoscopy is preferred for the identification and management of nonpalpable testes. A study by Samadi et al. [19] involving 173 patients and 203 procedures found that 58% of the testicles were located high in the abdominal cavity, 22% were low in the abdomen, 16% were peeping, 3% were intracanicular, and 1% were located behind the bladder [19]. El-Anany et al. introduced a system for categorizing laparoscopic findings of impalpable testes to aid treatment decisions [20]. Their study showed that 41.9% of cases involved high abdominal testes and 24.7% involved the internal ring without vas deferens looping. Cimsit et al. suggested that susceptibility-weighted imaging could help detect deep infiltrating endometriosis, potentially applicable in some cases of cryptorchidism [21].

4.3. Management of Paraneoplastic Anti-NMDAR Encephalitis

The detection of anti-NMDAR AE involves the identification of autoantibodies against anti-NMDAR in the cerebrospinal fluid or serum. Management includes tumor removal (if present) and immunotherapy, such as intravenous immunoglobulin, corticosteroids, and plasmapheresis [22, 23]. With prompt treatment, 66-80% of patients can recover most of their baseline neurological function, although this may take years. Approximately 20% of patients develop lasting deficits or do not survive the disease. Within two years of onset, approximately 10% of patients experience recurrence [24].

Combining multiple therapies yields better results than single therapy approaches for anti-NMDAR AE [25]. The approach to treating paraneoplastic syndromes, including anti-NMDAR AE, emphasizes early tumor removal and rapid immunosuppressive therapy. Immune checkpoint inhibitors could benefit certain cases of autoimmune encephalitis, particularly in tumors with high PD-L1 expression. Second-line agents targeting B cells, such as obinutuzumab or bortezomib, are being investigated for rituximab-resistant patients to achieve better B cell depletion or to target plasma cells.

The patient's treatment protocol, which included tumor excision, corticosteroids, rituximab, and plasmapheresis, followed this strategy. The treatment sequence may have influenced these outcomes. One study found that patients receiving intravenous immunoglobulin after therapeutic plasma exchange fared better than those who received intravenous immunoglobulin before therapeutic plasma exchange [26]. Early initiation of therapeutic plasma exchange appears to be advantageous in certain cases [26]. The patient's treatment plan was in accordance with current guidelines. However, further research is required to determine the optimal order and timing of these interventions. In cases that are unresponsive, alternative therapies such as intrathecal methotrexate, methylprednisolone, or bortezomib may be explored [27–29], although further studies are needed to establish their effectiveness and safety profiles.

The combination of cisplatin, etoposide, and ifosfamide has proven effective in treating mixed GCTs. The VIP (etoposide, ifosfamide, cisplatin) protocol has shown promising results in studies of GCTs, including diverse his-

tological types [30, 31]. Bleomycin, etoposide, and cisplatin regimens have demonstrated excellent efficacy and manageable toxicity in patients with malignant ovarian GCT [32]. Some protocols use carboplatin instead of cisplatin, particularly for high-dose treatments with autologous bone marrow rescue [33, 34]. The combination of cisplatin, etoposide, and ifosfamide is widely recognized as a treatment for mixed GCTs. However, the best therapeutic approach may vary based on the tumor site, disease stage, and prior treatments. Studies have confirmed the effectiveness of this regimen, with response rates ranging from 25 to 70% across different patient groups [30, 31, 35]. Research continues to improve treatment protocols and address the side effects of chemotherapy regimens.

Post-surgery studies have shown that abdominal testicles exhibit greater volume than those retained in the inguinal region, potentially due to prolonged exposure to abdominal temperature. Complications associated with the Torek method, including atrophy and structural changes, emphasize the need for ongoing evaluation of surgical methods [36]. These issues underscore the preference for contemporary procedures with improved outcomes. These findings align with research suggesting that timely intervention enhances testicular function, as early procedures are associated with better preservation of germ cell potential and a reduced risk of cancer [37, 38].

4.4. Role of Rituximab in AE Treatment

In adolescents with AE and GCTs, rituximab, an anti-CD20 monoclonal antibody, plays a crucial role in modulating the immune response. It accelerates neurological recovery by targeting B cell-driven autoimmune processes, particularly in patients with anti-NMDAR AE. Research supports rituximab's effectiveness in enhancing neurological outcomes through B-cell depletion [39–41]. This approach targets pathological B cells that produce antibodies against neuronal surfaces such as NMDA receptors [40]. The rapid clinical recovery aligns with the findings on rituximab's role in functional improvement and reduced relapse rates [39, 41, 42].

The treatment involved rituximab administration after tumor removal and initial immunotherapy, including corticosteroids and plasmapheresis. Rituximab, a monoclonal antibody targeting CD20 on B lymphocytes, is a key component of anti-NMDAR AE immunotherapy. By eliminating B cells, rituximab disrupts autoantibody production and alters the immune response through changes in antigen presentation. Its effectiveness increases with the use of corticosteroids and plasmapheresis, which reduce inflammation and remove circulating autoantibodies. In this series, triple therapy resulted in rapid clinical recovery and sustained remission in all patients. Each case showed a swift improvement with tailored interventions. Rapid symptom resolution aligns with studies showing that early rituximab use leads to neurological improvement [42]. These cases highlight the need for multidisciplinary surgical, chemotherapeutic, and immunomodulatory treatments. Rituximab, when combined with other therapies, improves outcomes, especially in pediatric cases [41, 43]. Incorporating rituximab into the comprehensive treatment of AE associated with GCTs aids in their management [39, 44].

Early screening and surgical referral protocols are required to facilitate timely treatment and to reduce the risk of infertility. Evidence suggests that immune dysregulation in the testes is linked to systemic autoimmunity, particularly in GCTs associated with cryptorchidism. The testis, an immune-privileged site, may lose protection due to elevated intra-abdominal temperatures and compromised blood-testis barriers in undescended testes. These changes enable antigen leakage and immune cell infiltration, thereby activating autoreactive cells against germ cell antigens. Paraneoplastic neurological syndromes can develop when the immune response targets neuronal epitopes, informing the development of biomarker-driven immunotherapies for detection and treatment.

5. Limitations and Future Directions

This study highlights the importance of ongoing research, particularly longitudinal investigations to monitor reproductive outcomes in adulthood and molecular studies to elucidate the genetic predispositions associated with cryptorchidism. The findings of this study will contribute to the improvement of treatment strategies and the enhancement of long-term reproductive health outcomes in individuals with cryptorchidism.

This study contributes to pediatric urology by documenting the surgical outcomes of early orchiopexy using different techniques. The primary impact of this study is the detailed description of three pediatric cases of GCTs with paraneoplastic anti-NMDAR AE. The use of rituximab as a therapeutic agent provides insights into the management of paraneoplastic AE. These findings suggest the potential application of B-cell depletion strategies in pediatric autoimmune neurological disorders. However, the small number of AE cases and the lack of long-term

immune monitoring limit definitive conclusions about the outcomes of rituximab-based treatment.

This study has several limitations. Although the study had a substantial sample size, its focus on two specialized facilities in Kyrgyzstan could restrict its applicability to wider populations with differing healthcare systems and genetic makeups. The absence of long-term reproductive outcome data is a drawback, as the research primarily focused on immediate surgical success, testicular size, and DUS findings. The lack of post-puberty semen analysis and endocrine evaluations hinders a complete assessment of the impact of surgical intervention on future fertility. Although various surgical techniques have been examined, the non-randomized selection of methods could have affected the outcomes owing to differences in surgeon expertise and patient-specific considerations. Future research should include prospective multicenter trials with extended follow-up periods to allow for a thorough evaluation of the long-term effects of early orchiopexy on fertility and testicular function.

6. Conclusion

This study emphasizes the importance of early detection and treatment of cryptorchidism to reduce the risks of infertility and testicular cancer. Orchiopexy before the age of three years leads to better testicular volume and function, emphasizing the need for timely intervention according to international guidelines. This study examined the immunological aspects of cryptorchidism-related TGCT and their link to paraneoplastic AE beyond surgical factors. Rituximab-based immunotherapy for anti-NMDAR encephalitis demonstrates the value of B-cell depletion strategies. The combination of rituximab with corticosteroids, plasmapheresis, and chemotherapy led to neurological improvement, demonstrating the effectiveness of multimodal immunotherapy. Early detection of anti-NMDAR antibodies aids in the diagnosis of paraneoplastic autoimmune encephalitis in young patients with cryptorchidism and neurological symptoms. Immune monitoring is needed after TGCT removal. Future research should investigate the immunogenetic basis of cryptorchidism-associated GCTs, focusing on the breakdown of immune privilege and the development of autoimmunity. Long-term monitoring is essential for evaluating recovery after surgery and immunotherapy. These findings emphasize the need to combine surgical, oncological, and immunological expertise to improve outcomes in infants with cryptorchidism.

Author Contributions

Conceptualization, A.E., and T.O.; methodology, B.E.; software, V.P.; validation, B.D.O., and C.T.; formal analysis, S.E.; investigation, S.E., T.O., B.E., and V.P.; data curation, B.D.O.; writing—original draft preparation, C.T., S.E., and Y.V.; writing—review and editing, Y.V. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Bioethical Committee of I.K. Akhunbaev Kyrgyz State Medical Academy (Protocol No. 9, dated January 22, 2022).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

Data are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare no conflict of interest.

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