A RARE CASE OF COMBINATION TRICHORINOPHALANGEAL SYNDROME AND MAYER–ROKITANSKY–KÜSTER–HAUSER SYNDROME

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Two forms of Mayer–Rokitansky–Kuster–Hauser (MRKH) syndrome are recognized: isolated uterovaginal agenesis and associated with extragenital malformations, including several well-recognized syndromes. Trichorhinophalangeal syndrome (TRPS) is a rare autosomal dominant condition characterized by facial dysmorphism, ectodermal and skeletal features. TRPS comprises TRPSI (caused by a heterozygous pathogenic variant in TRPS1), TRPSII (caused by contiguous gene deletion of TRPS1, RAD21, and EXT1). Genital anomalies occur particularly in TRPSII. We present a case of rare combination TRPSII with MRKH syndrome. Delayed diagnosis resulted to prolonged pain syndrome and repeated surgery. Recognition of genital anomalies in TRPS allows timely referral diagnosis and appropriate care by paediatrician and adolescent gynaecologists.

Keywords: trichorhinophalangeal syndrome, urogenital anomaly, MRKH syndrome

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РЕДКИЙ СЛУЧАЙ СОЧЕТАНИЯ ТРИХОРИНОФАЛАНГЕАЛЬНОГО СИНДРОМА И СИНДРОМА МАЙЕРА–РОКИТАНСКОГО–КЮСТЕРА–ХАУЗЕРА

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Выделяют два варианта синдрома Майера–Рокитанского–Кюстера–Хаузера (MPKX): тип I, при котором наблюдается изолированная аплазия матки и влагалища, и тип II, при котором имеют место сопутствующие экстрагенитальные пороки развития, в рамках некоторых синдромальных состояний. Синдром Лангера–Гидеона или трихоринофалангеальный синдром (TRPS) — редкое аутосомно-доминантное заболевание, характеризующееся лицевым дисморфизмом и аномалиями кожи, ногтей и волос. Выделяют два типа трихоринофалангеального синдрома: TRPSI, обусловленный патогенным вариантом гена TRPSI, и TRPSII, обусловленный делецией с вовлечением генов TRPS1, RAD21 и EXT. Как правило, пороки развития половых органов встречаются при типе II. Представлено клиническое наблюдение TRPSII в сочетании с MPKX. Отсроченная диагностика порока развития половых органов привела к длительному болевому синдрому у пациентки с крайне отягощенным анамнезом и проведению неоднократных хирургических вмешательств. Своевременное обнаружение сочетания аномалий половых органов у девочек с TRPS позволяет не только установить диагноз, но и оказать квалифицированную помощь с участием гинеколога детей и подростков, с целью минимизации возможных осложнений.

Ключевые слова: трихоринофалангеальный синдром, аномалия мочеполовых органов, MPKX-синдром

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The MRKH syndrome (OMIM 277000) is a rare condition with prevalence of about 1 in 5,000 women. It is characterized by the absence or hypoplasia of the uterus and the upper two thirds of the vagina in 46,XX females [1–3]. This malformation can occur isolated or with various anomalies, with a relatively common subset of these comprising Müllerian, renal, and cervicothoracic abnormalities (MURCS association) [2].

Occasionally, MRKH was combined with situs viscerum inversus, Dandy–Walker malformation, Meckel–Gruber syndrome, Bardet–Biedl syndrome, Cornelia de Lange syndrome, Holt–Oram syndrome or McKusick–Kaufman syndrome [1, 2]. However, it can probably be explained by simple coincidence. To our knowledge, the genetic causes of MRKH remains unknown.

Trichorhinophalangeal syndrome was first reported by A. Giedion in 1966, described in more detail by L.O. Langer in 1969 [3, 4]. The population frequency is less than 1 : 1,000,000. It is characterized by severe craniofacial and skeletal abnormalities. Patients with trichorhinophalangeal syndrome usually have a specific skull structure with sparse and slowly growing hair on the head, protruding ears, sparse eyebrows, a convex pear-shaped nose, thin lips, elongated chin, and bone anomalies, including mild to severe brachydactyly, hip dysplasia and short stature [3–8]. Additionally, female patients may have urogenital anomalies [3, 4, 8].

TRPSII or Langer-Giedion syndrome (OMIM 150230) associated with contiguous 8q23.3q24.11 deletion that spans

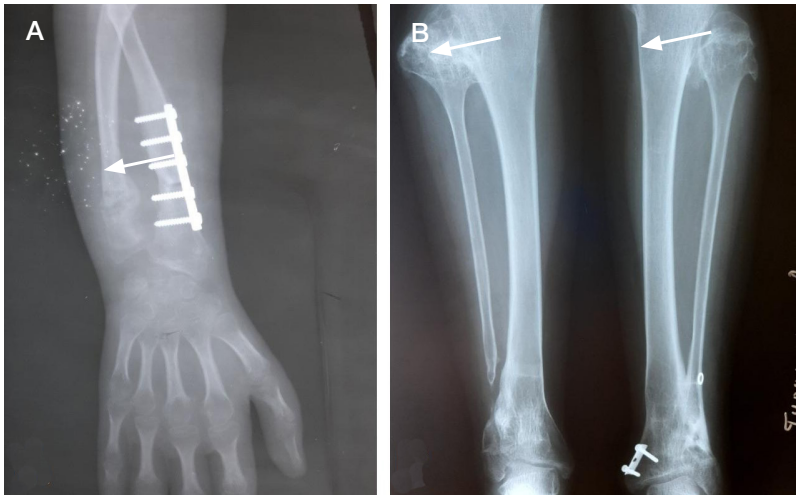

Fig. 1. X-ray picture of the bones of the upper (**A**) and lower (**B**) extremities with multiple exostoses (*shown by arrows*) and metal structures after surgery

the TRPS1-EXT1 interval [2–7], more often diagnosed using chromosomal microarray.

Chromosomal microarray analysis (CMA) is designed to detect microscopic and submicroscopic copy number variations (CNVs) across the genome [9, 10]. Recent guidelines and publications have recommended CMA for the evaluation of children with autism spectrum disorders, developmental delay/intellectual impairment, and/or multiple congenital anomalies [11–15]. CNVs are observed in up to 20% of cases with genital tract malformations [16]. Nik-Zainal et al. reported 14% prevalence of CNVs in a cohort of patients with isolated and syndromic Müllerian aplasia [15].

Unfortunately, limited publications, describing a combination of TRPS and Müllerian anomalies, complicate early diagnosis [8].

Clinical case description

A 14-year-old girl with a known medical history of TRPSII was referred to the National Medical Research Center for Obstetrics, Gynecology and Perinatology for primary amenorrhea and progressively increasing cyclic lower abdominal pain.

The girl was the first child of a non-consanguineous couple and had a younger healthy brother. Her medical history, obtained from her parents, included spontaneous delivery from first uneventful pregnancy, with a birthweight of 3,600 g, and length 52 cm. At 2 days of age, she was transferred to neonatal intensive care unit due to the lack of sucking and absent swallow reflexes. Subsequently, the girl presented with a delay in physical and mental development, she was characterized by dysplastic body shape, pronounced facial characteristics and shortening of the hands and feet. At the age of 3 years, the TRPSII was diagnosed, but the genetic result was lost.

Since 4 years of age, the girl presented with tumor-like formations in the proximal sections of both humerus, distal forearm, femur, and articular ends of both tibiae. The patient underwent 27 surgical interventions due to deformations of the extremities, associated with multiple exostoses (Fig. 1).

In December 2018, she was hospitalized with severe abdominal pain. The laparoscopic cystectomy of the left ovary and appendectomy were performed. No abnormalities of the genital tract were observed. After discharge from the hospital, the patient suffered cyclic, progressively increased, lower abdominal pain. The parents sought care from our department of pediatric and adolescent gynecology, as there was no improvement under the conservative therapy (non-steroidal anti-inflammatory drugs, gestagens).

The condition of the girl upon admission was stable, with height 144 cm and weight 40 kg. Sexual development was described

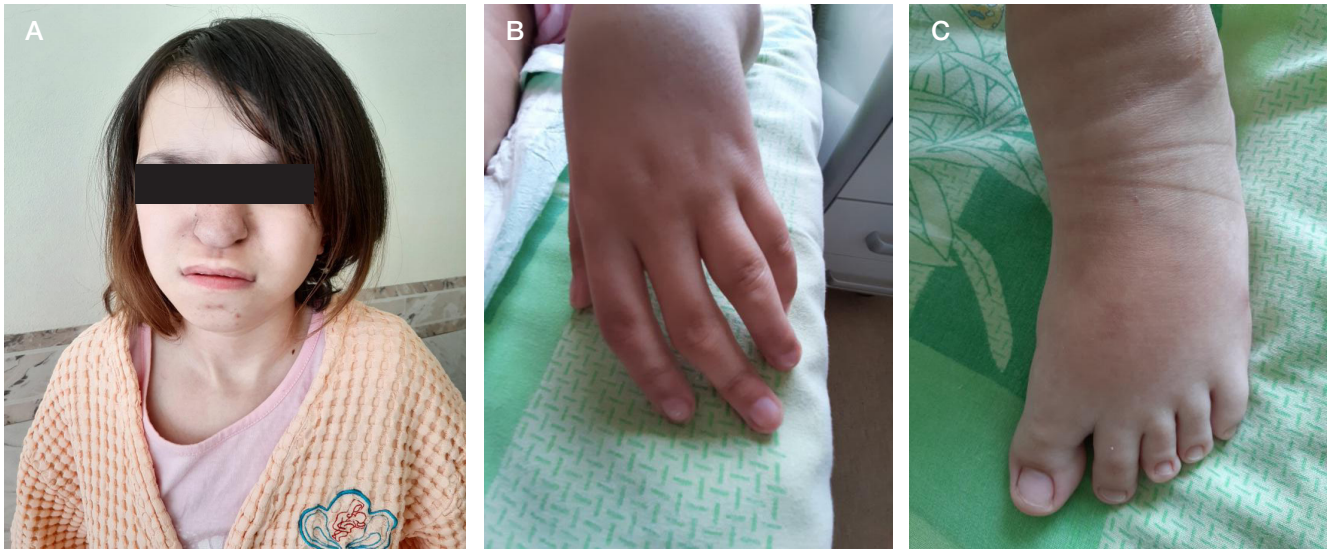

Fig. 2. Typical dysmorphic features of the patient: slowly growing hair, a long pear-shaped nose with a bulbous tip (**A**) shortening of the hands with enlargement of interphalangeal joints (**B**) and feet (**C**)

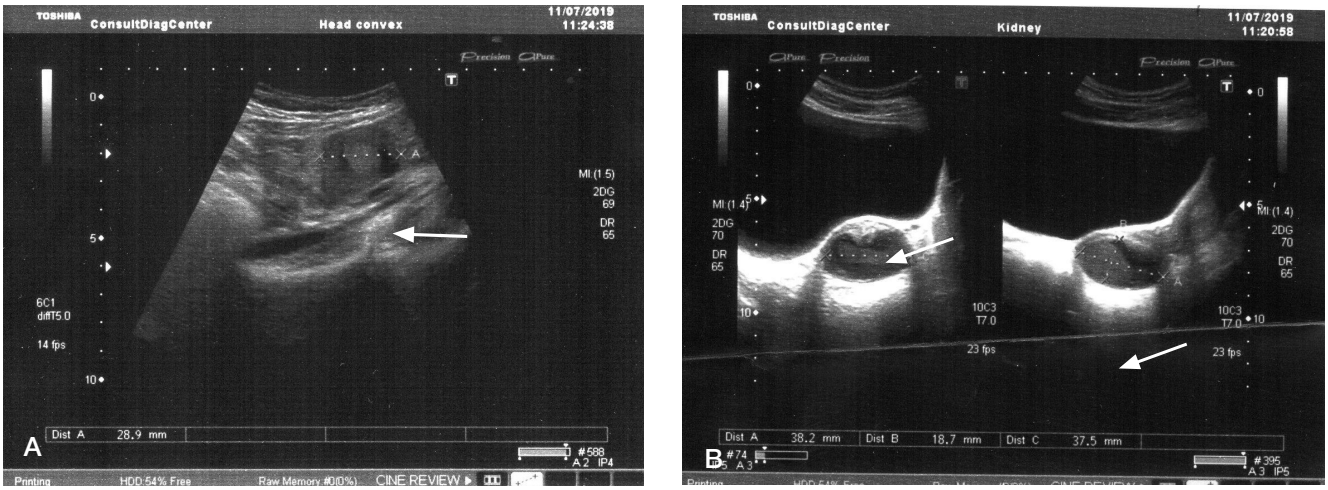

Fig. 3. Transabdominal ultrasound examination: **A** — rudimentary uterine rudiment (transverse scanning); **B** — the same structure in longitudinal scanning

as Tanner 3. She had a dysplastic physique characterized with multiple deformities of the upper and lower extremities, a long pear-shaped nose, lower jaw hyperplasia, large protruding ears and multiple cartilaginous exostoses (Fig. 2).

The gynecological examination revealed normal external female genitalia, hymen fringed, behind the hymen there was a blind ending vaginal fossa to 1.0 cm. During recto-abdominal examination, the uterus was characterized by spherical shape, tender to the palpation. Laboratory parameters of the patient, including hormonal status, were all within normal values.

Following genetic counseling, CMA determined a pathogenic 6,9 Mb deletion at chromosome 8q23.3-q24.12 (115,524, 782–122,445,687 bp, GRCh37) with the involvement *TRPS1*, *EXT1*, and *RAD21* genes, and a duplication on the long arm of chromosome 18 (18q12.3) over 2.8 Mb of unknown clinical significance. The genetic results confirmed TRPS II syndrome.

Study of both parents revealed that the patient's deletion was «*de novo* » in origin. The father carried the 18q12.3 duplication; therefore, its contribution to the girl's phenotype is unlikely, and it was considered to be likely benign.

An MRI of the pelvic organs was not possible due to the presence of multiple metal structures. Ultrasound examination of the pelvic organs in our center revealed a spherical structure consistent with a uterus, displaced to the left and upwards with dimensions 38 × 27 × 29 mm, and 3 mm endometrium, the ovaries were located high in the pelvic cavity but there was no identifiable cervix and vagina (Fig. 3).

Due to the cyclic pain syndrome, combined with the ultrasound findings, an obstructive anomaly of the Müllerian tract was suspected. The laparoscopy revealed two uterine rudiments, each located at the sidewalls of the pelvis, connected by a cord over the bladder. The left rudiment had signs of functioning; the right rudiment recognized as a small muscle nubbin, connected with the round ligament of the uterus and fallopian tube. The cervix and vagina were absent (Fig. 4).

Despite of the size, the left uterine rudiment was a structure without cervix. In this case, a surgical creation of the utero-vaginal anastomosis was considered impractical due to high-risk complications and other patient's health problems. Multidisciplinary team, including ethics specialists, decided to remove the uterine rudiments. The parental consent was obtained. Postoperative period was uneventful and the girl was discharged home in a satisfactory condition. At the one-month and three-month follow-up visits, her parents reported complete resolution of the pain syndrome.

Clinical case discussion

LGS includes the clinical features of TRPS type I, caused by the haploinsufficiency of *TRPS1*, and multiple hereditary exostoses due to deletion EXT1 [16–18]. Some reported patients have been also characterized with the clinical features of Cornelia de Lange syndrome, type 4 [19,20]. In addition to findings of TRPSII, Müllerian aplasia was ascertained in our proband. Syndromic Mullerian aplasia may be linked to 17q12 microdeletion [21], 1q21.1 microduplication, Xq21.31 microdeletion [22]. Furthermore, several cases of Müllerian

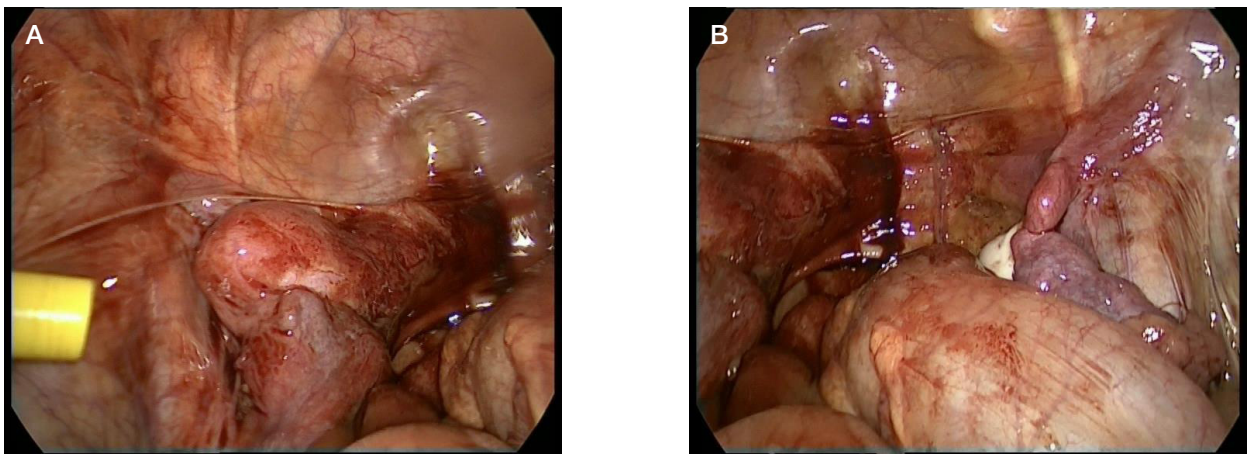

Fig. 4. Laparoscopic view of the internal genital organs: left uterine rudiment with signs of functioning (**A**); right uterine rudiment (muscle nubbin) (**B**)

aplasia in patients with 16p11.2 microdeletion are described in the literature [23]. Mullerian duct remnants are also occasionally associated with TRPS [24].

Other genital abnormalities in patients with TRPS II were reported in previous studies. One reported a woman with vaginal atresia and hematometra with 8q24.11–q24.12 deletion [19]. Another showed a girl with persistent cloaca and prune belly sequence and 8q24.11–q24.13 deletion [20]. Fryns et al. reported hydrometrocolpos in three children with 8q24.11–q24.13 deletion [21]. Plaza-Benhumea et al. described a 19-year-old female with imperforate hymen, severe vaginal stenosis and hematometra with 8q23.3-q24.12 deletion [25].

In our patient 8q23.3q24.12 deletion, approximately 6.9 Mb, affects *TRPS1*, *EIF3H*, *RAD21*, *SLC30A8*, *MED30*, *EXT1*, *TNFRSF11B*, *COLEC10*, *MAL2*, *NOV*, *ENPP2*, *TAF2*, *DSCC1*, *DEPTOR*, *COL14A1*, *MRPL13*, *MTBP*, and *SNTB1* genes. It is interesting, that pathogenic variants in RAD21 have been associated with Cornelia de Lange syndrome type 4, which characterized with variable congenital anomalies, including genitourinary malformations, intellectual disability, distinctive facial features [26–28]. So, in our opinion, *RAD21* can be a good candidate for MRKH syndrome, which requires further research.

CONCLUSION

Female patients with TRPS II would benefit from a multidisciplinary approach with geneticist, pediatrician and adolescent gynecologists in order to allow early detection of Müllerian anomalies.

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