CASE REPORT

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Ovarian teratomas in a patient with Bardet–Biedl syndrome, a rare association

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Abstract

Bardet–Biedl syndrome (BBS) represents a rare ciliopathy recessive autosomal inherited. The main clinical features are retinal dystrophy, postaxial polydactyly, obesity, different degrees of cognitive deficit, renal impairment, hypogonadism and genital malformations. The genetic explanation consists in BBS genes mutations, which encode modified proteins, altering the function of the immotile cilia. As a multitude of BBS genes mutations were described, the phenotypic aspect of these disorders varies according to that. We present the case of a 22 years old female patient, known with BBS since the age of 11 and which was diagnosed and operated for bilateral ovarian dermoid cysts, at the age of 21. We did not find a similar case in literature, regarding the association between the two disorders. We consider that our case points towards the importance of periodic imagistic evaluations [magnetic resonance imaging (MRI), computed tomography (CT) or ultrasound] of these patients, not only clinical and biological. Usually, the moment they are diagnosed with hypogonadism or genital malformations (in childhood or adolescence), the genital evaluation is neglected thereafter. We also consider that our therapeutic approach can be helpful in other similar clinical situations. Another important conclusion is represented by the importance of genetic counseling of the relatives of a BBS patient, unfortunately insufficiently provided in our region.

Keywords: Bardet–Biedl syndrome, retinal dystrophy, hypogonadism, dermoid cysts, ovaries.

Introduction

Bardet–Biedl syndrome (BBS) represents a rare genetic disorder with autosomal recessive transmission. Its prevalence varies, according to *National Library of Medicine* (US)–*Genetics Home Reference*, from Bedouin population in Kuwait (1:13 500) and Canada (1:17 500) to Europe (1:160 000) and Japan (only 38 possible cases in 2011) [1, 2]. Even if in the beginning, it was named Laurence–Moon–Bardet–Biedl syndrome and thereafter separated into two entities: Laurence–Moon and Bardet–Biedl, now the consecrated term is BBS.

The major clinical expression of BBS is represented by retinal dystrophy, post-axial polydactyly, obesity, different degrees of cognitive deficit, renal impairment and hypogonadism. Many other disturbances can occur, like genital malformations, facial dysmorphysm, disorders of posture and gate, etc. [3]. They are not all found in the same patient and they do not have the same expression in all the patients, probably because at least 20 different genes (called BBS genes) show mutations in different combinations [4, 5].

Cilia are cellular structures with tubular aspect found on the apical surface of the majority of the cells and they are involved in cell movement (motile cilia) and in chemical signaling pathways (immotile cilia). Cilia are also necessary for the perception, acting like sensory organelle.

The mutated BBS genes encode modified proteins, which in turn alter the function of immotile cilia. Immotile cilia are clinically translated into retinitis pigmentosa, renal, hepatic and pancreatic cysts, polydactyly, learning difficulties [6].

The rate of survival of these patients rarely exceeds 60 years old but studies are limited in this field. Some of them are depicting a median survival of 63 years [7], others are presuming less than that [3].

Dermoid cysts represent germ cell tumors containing different tissues developed from one or all three germinative layers, most frequently from the ectodermic layer. Because of their germinal origin, they are frequently found in the gonads, ovaries in the first place. The dermoid cysts and teratomas are in the majority of cases the same entity. Teratomas can be mature, well differentiated and benign, usually with cystic appearance, or immature, mainly solid and malignant. Their treatment is surgical, with significant possible complications and morbidity [8].

We present for the first time, up to our knowledge, a case of BBS associated with ovarian teratomas. We found other cases of teratomas associated with Bardet–Biedl syndrome but with different locations and different treatment options [9].

Patient's legal tutor written approval was obtained in order to publish the case.

Case presentation

A 20-year-old patient came in consultation for hypermenorrhea, menorrhagia, irregular menses and pallor in the II[nd] Medical Department of the Railways Hospital, Constanţa, Romania, in 2014.

Her familial history revealed that she had a younger sibling who was diagnosed with BBS (he died at the age of eight, due to chronic renal failure) and that she has a cousin with BBS, also.

Until the age of 11 years old, she was not evaluated for BBS even if she was born with bilateral lower limbs polydactyly (surgically removed at one year of age), and even if her younger brother was already diagnosed with this disorder, before she turned 11.

She was diagnosed with BBS at 11 years old, when she was endocrinological evaluated for obesity [height 160 cm and weight 77 kg; body mass index (BMI) 30 kg/m^2], visual impairment, brachydactyly, mild learning disability. She started to lose her night vision at the age of 9 and now she is able to detect only light. At that time, the check-up revealed dyslipidemia (serum cholesterol 265 mg/dL, triglycerides 483 mg/dL), subclinical hypothyroidism [thyroid-stimulating hormone (TSH) 6.8 µIU/mL, without autoimmunity], altered oral glucose tolerance test (OGTT) but with a normal value of HbA1c (glycosylated hemoglobin) and mild spasticity of the lower limbs (Table 1). Diet and 50 µg of L-Thyroxine/day were recommended as well as further investigations in a specialized service.

Table 1 – ***Patient's biological and humoral parameters over time***

Age [years]	***11***	***12***	***16***	***20***	***21***	***22***
L-Thyroxine treatment [µg/day]	***Without treatment***	***50 µg L-Thyroxine***	***50 µg of L-Thyroxine***	***50 µg of L-Thyroxine***	***75 µg of L-Thyroxine***	***90 µg of L-Thyroxine***
Height [cm]	160	164	168	170	170	170
Weight [kg]	**77**	**85**	**84**	**76**	**75**	**75**
BMI [kg/m^2]	**30**	**31.6**	**28.8**	**26.3**	**26**	**26**
Glycemia à jeun (60–99 mg/dL)	**123**	74	86	84	87	101
OGTT [mg/dL]	**201** at 1 h **182** at 3 h **155** at 4 h	106 at 1 h 99 at 2 h 100 at 3 h	–	–	–	–
Creatinine (0.6–1.2 mg/dL)	1.21	1.1	0.9	1.03	1.02	0.81
Urea (<43 mg/dL)	25.3	22.5	23	38	36	35
Total cholesterol (<200 mg/dL)	**265**	191	220	**263**	**254**	**301**
Triglycerides (<150 mg/dL)	**483**	**215**	200	95	**160**	118
FSH (children <5.1 mIU/mL; adult women 3.5–12.5 mIU/mL)	0.41	–	–	5.2	5.6	–
LH (children 0.2–1.4 mIU/mL; adults 2–12.6 mIU/mL)	0.19	–	–	**20.6**	**24.1**	–
Progesterone – luteal phase (5.3–86 nmol/L)	–	–	–	**0.67**	**0.59**	**0.57**
Estradiol – follicular phase (46–607 pmol/L)	–	–	52.7	180.1	230.3	–
TSH (0.51–4.3 µIU/mL)	**6.8**	1.6	2.53	**6.99**	**5.45**	1.1
ATPO (<50 IU/mL)	10.6	–	–	16.5	–	–
AbTGB (<115 IU/mL)	–	–	–	60.3	–	–
FT4 (0.8–2.02 ng/dL)	**0.6**	1.4	–	0.8	1.2	–
Prolactin (72–511 µIU/mL)	–	–	183	173	–	251.9
17-OH-KT (3–12 mg/24 h)	–	4.02	–	–	–	–
17-KT (3.3–11.5 mg/24 h)	–	7.8	–	–	–	–

BMI: Body mass index; OGTT: Oral glucose tolerance test; FSH: Follicle-stimulating hormone; LH: Luteinizing hormone; TSH: Thyroid stimulating hormone; ATPO: Anti-thyroid peroxidase antibodies; AbTGB: Anti-thyroglobulin antibodies; FT4: Free tetraiodothyronine; 17-OH-KT: 17-OH-ketosteroids; 17-KT: 17-Ketosteroids. Abnormal data are in bold.

She repeated a clinical and lab check-up, one year later (at the age of 12). She had, while treated, BMI 32 kg/m^2, normal OGTT, hypertriglyceridemia (215 mg/dL), normal TSH (1.6 µIU/mL). Hypothalamic-hypophyseal computed tomography (CT) scan revealed empty sella with frontal cortical atrophy. Gonadal and suprarenal functions were evaluated at that moment and found within normal limits (Table 1). Abdominal CT scan did not reveal any renal malformations. Ophthalmological evaluation established the diagnosis of atypical retinitis pigmentosa. Diet, L-Thyroxine and periodic evaluations were recommended.

Menarche occurred at 14 years old.

At 16 years old, her biological parameters confirmed the persistence of dyslipidemia (serum cholesterol 220 mg/dL and triglycerides 200 mg/dL) and the normalized thyroid function (TSH 2.53 µIU/mL, under treatment). Renal ultrasound and functional evaluation where within normal limits, too.

Until the age of 20, she was not evaluated any further – until menstrual disorders occurred and the patient presented in our Department. She kept, all the same, a healthy hypocaloric, hypolipidemic diet, rich in vegetables, fruits and lean meat.

Physical examination revealed facial dysmorphism with flat nose bridge and with anteverted nares, downward slanting palpebral fissures, high arched palate, small teeth and enamel hypoplasia, normal height (170 cm) and overweight (76 kg). She has brachydactyly and brachymetacarpia, especially in the 4th and 5th fingers, multiple skin nevi on the thorax and abdomen, micromastia, normal sexual body hair. She has mild ataxia, lateral nystagmus, and the mild spasticity of the lower limbs persists (Figure 1).

During her endocrinological work-up, we found low levels of progesterone in luteal phase, a luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio of almost 4 in early follicular phase, subclinical hypothyroidism (under treatment with 50 μg of L-Thyroxine/day) and a cystic aspect of the ovaries at trans-abdominal ultrasound (virgo patient who refused ultrasound examination with intra-rectal probe). L-Thyroxine was increased gradually up to 90 μg/day and TSH values were normalized. Dydrogesterone 20 mg/day 10 days per menstrual cycle was started. Under this treatment, menses became regular, with a five days duration and normal flow, occurring at 28–29 days. After nine months of treatment, the patient stopped her progestin treatment and bradymenorrhea occurred. The LH/FSH ratio was 4.3 and the ultrasound revealed that cystic ovarian aspect maintained but they seemed to modify their inner aspect (hyperechoic areas, even calcifications). She was HIV (human immunodeficiency virus) negative. Pelvic magnetic resonance imaging (MRI) was performed and revealed polycystic ovaries and the suspicion of bilateral ovarian dermoid cysts also, of 2.1 cm and 7.2 mm in diameter (Figures 2 and 3).

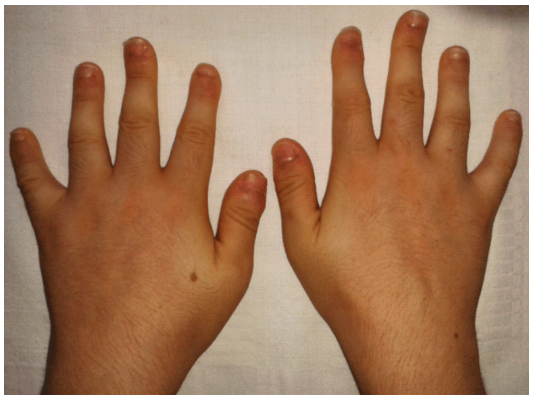

Figure 1 – ***Brachydactyly of the IVth and Vth finger.***

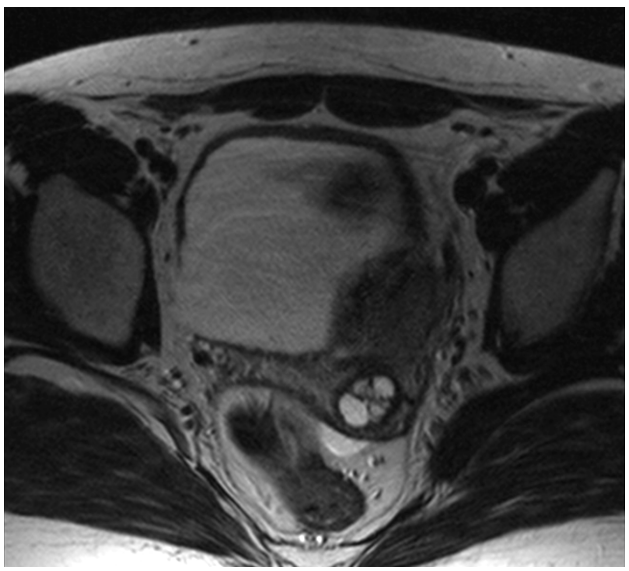

Figure 2 – ***Pelvic MRI: left ovary dermoid cyst.***

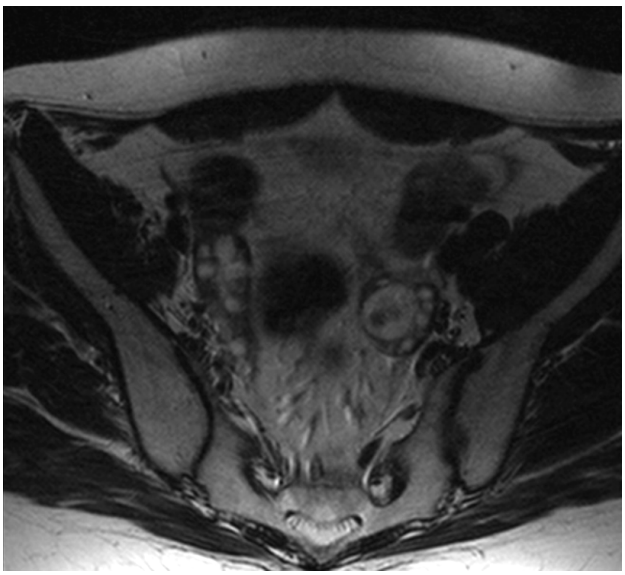

Figure 3 – ***Pelvic MRI: bilateral polycystic aspect of the ovaries.***

Laparoscopic surgery was performed in the Ist Gynecology Department of the Emergency County Hospital of Constanţa and two ovarian cysts, one on each side and one paraovarian cyst on the left were removed (Figures 4–7).

Histopathological examination was performed in the Department of Pathology of the Emergency County Hospital of Constanţa and the presence of mature bilateral teratoma along with one simple cyst was confirmed. Patient's family asked for a second opinion so, two blocks were analyzed in the Department of Pathology of the "St. Pantelimon" Emergency Hospital, Bucharest, Romania. The results were the same: fragments of ovarian tissue along with sebaceous glands, pilous follicles, and cystic areas with parakeratotic pluristratified pavement epithelium; cellular detritus, squames, all confirming bilateral ovarian dermoid cysts (Figures 8–10).

Progestin and L-Thyroxine treatment were continued.

One year after, menses are regular, and ultrasound of the ovaries reveals simple cystic aspect. Renal function is normal and a mild dyslipidemia persists.

Discussion

Because the time between the onset of symptoms and signs and diagnosis is quite long (up to eight years in some studies) [7], the majority of BBS patients looking healthy at birth unless they were born with polydactyly, or because other symptoms of BBS gradually appear during or after the first decade of life, an attempt was made by Beales *et al.*, in 1999, to modify the existing diagnostic criteria of BBS, in order to help establishing an earlier diagnosis, especially in children [3].

These criteria are divided into six primary: rod-cone dystrophy, polydactyly, obesity, renal defects, genital abnormalities and learning difficulties and secondary features: developmental delay, speech deficit, brachydactyly or syndactyly, dental defects, ataxia or poor coordination, olfactory deficit, diabetes mellitus, and congenital heart disease. Four primary or three primary and two secondary criteria are necessary to establish the diagnosis of BBS [6, 7].

Even if BBS gene testing was not available for us, the clinical criteria of diagnosis are fulfilled by our patient.

These are: macular dystrophy, polydactyly, obesity, learning difficulties – as major criteria and brachydactyly, and slight ataxia – as a secondary criteria. She has luteal insufficiency also, sustained by her FSH, LH and progesterone levels, as well as by the good menstrual response at progestins.

The age at diagnostic, 11 years, was older than the median of 8 found by the authors cited before [7], even if important clues were available: polydactyly at birth and a sibling diagnosed with BBS when our patient was 7 years old. We think that an earlier diagnosis might have improved the measures taken especially in reducing dyslipidemia and obesity as cardiovascular risk factors.

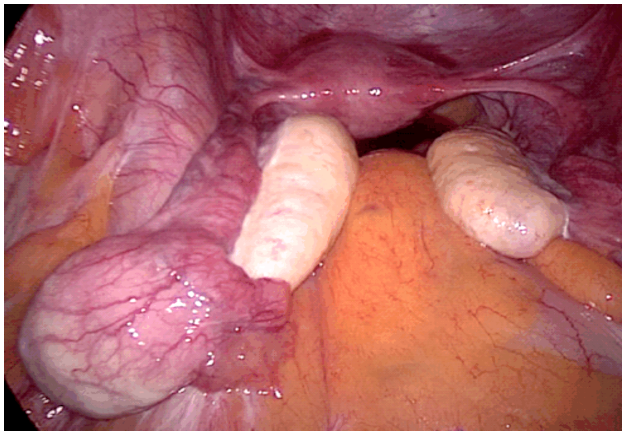

Figure 4 – ***Laparoscopic view showing normal (rather smaller) uterus, normal tubes, a para-ovarian cyst and slightly enlarged, elongated, ovaries.***

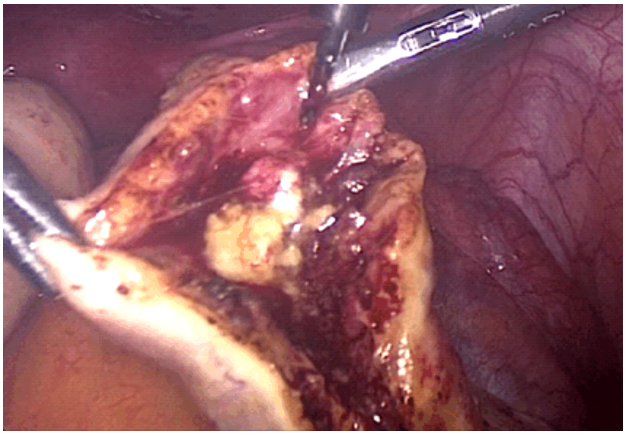

Figure 5 – ***Laparoscopic view showing fatty-sebaceous tissue inside the right ovary, during cystectomy.***

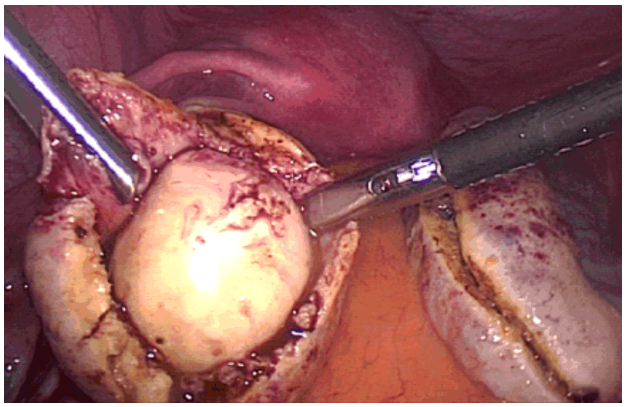

Figure 6 – ***Laparoscopic view showing the dermoid cyst within the left ovary, during the cystectomy.***

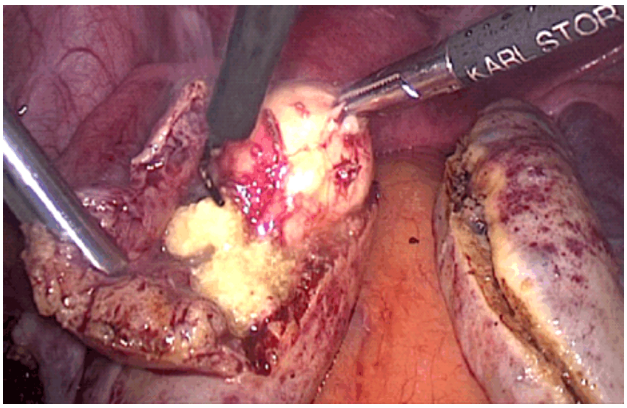

Figure 7 – ***Laparoscopic view showing expulsion of sebaceous-fatty tissue during the left ovarian cystectomy.***

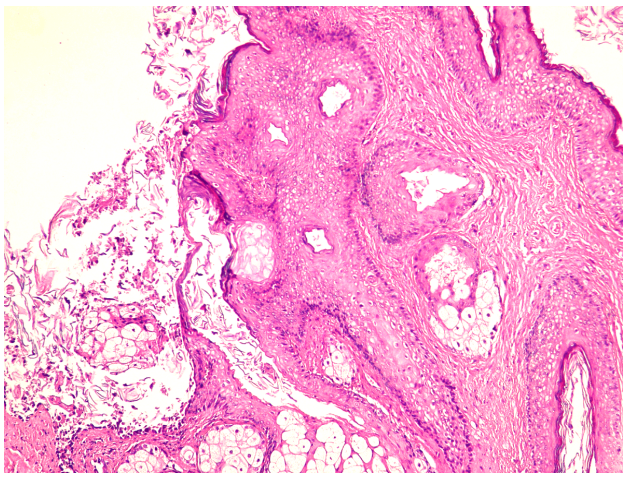

Figure 8 – ***Left ovarian dermoid cyst – pluristratified pavement epithelium with keratinization, sebaceous glands and pilous follicles. HE staining, ×200.***

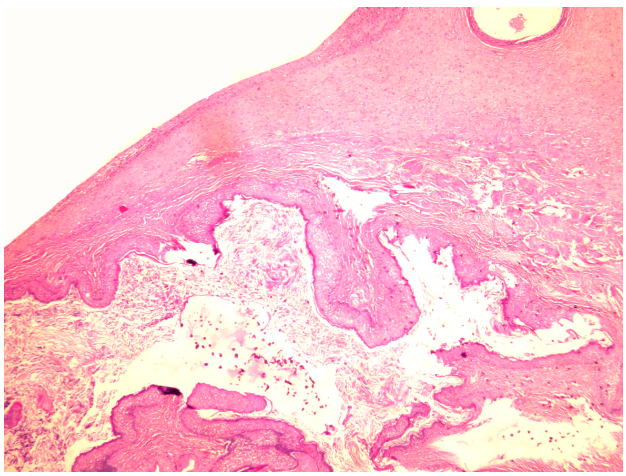

Figure 9 – ***Left ovary image with follicular cyst (upper right) and keritinized pluristratified epithelium and keratin squames inside the mature dermoid cyst. HE staining, ×40.***

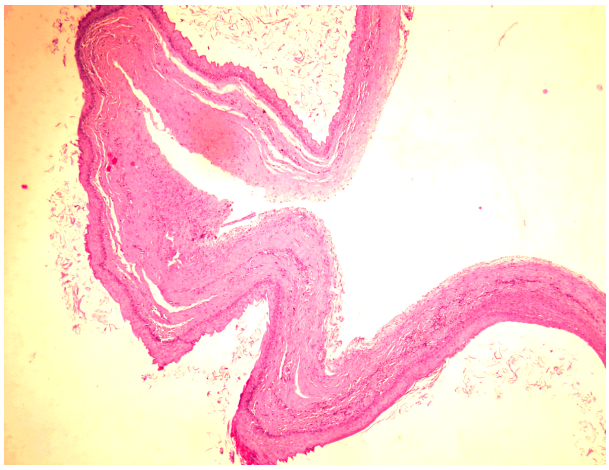

Figure 10 – ***Right ovarian dermoid cyst – ovarian tissue surrounded by keratotic pavement pluristratified epithelium which forms cystic areas with keratin content. HE staining, ×40.***

Anyway, we think that our patient has an attenuated form of the disease as her retinal dystrophy did not evolve in the last 3–4 years and she did not suffer any other worsening of her already known disorders. However, in order to sustain this hypothesis, a genetic test would be highly illustrative.

Available data is in favor of the frequent occurrence of renal impairment associated with BBS. This consists in renal cysts, renal scarring, hydronephrosis, fetal lobulated aspect, renal dysfunction up to renal failure, renal carcinoma, etc. [7, 10]. There are also proofs that renal malformations and renal carcinoma are frequent among the BBS-free relatives of BBS patients – and the explanation can be heterozygosity for BBS genes [7]. Sure, prenatal renal malformations are equally not relevant for this case [11, 12]. There is a study which report that first-degree relatives have no predisposition to metabolic and renal disorders [6] but the small number of subjects included in the study can be a bias. These findings have important implications for the care of BBS patients and their BBS-free relatives. This was the case of our patient's sibling, also. Fortunately, until now, our patient renal function is normal.

We did not find in the literature another report of a case of BBS associated with ovarian mature teratoma. We do not know if this is an occasional association or not. We consider, therefore, that periodic total abdominal and thoracic investigation (ultrasound, MRI), not only renal or cardiac, is necessary in order to detect tumor occurrence.

We choose to operate her for these tumors because of the possible future complications: atypical rapid growth (as they were not detected in the previous ultrasound examinations, even abdominal CT scans), torsion, even carcinomatous transformation [13]. HIV testing was considered appropriate as she lives in a region with a previous relatively high incidence of HIV infection [14].

Men with BBS are usually infertile [15] but a case of reversible hypogonadotrophic hypogonadism in a male who developed spontaneous reversal of hypogonadism in adulthood was reported [16]. Women have irregular menses and they may develop both gonadal failure and central hypogonadism [17]. There are rare cases reported with preserved fertility, probably those with incomplete gene penetration [7]. We assumed that an early menopause could occur due to ovarian surgery associated with usual premature ovarian failure found in these patients [7], but, fortunately, until this moment it did not.

For the moment, treatment options for patients with BBS are mostly symptomatic. However, gene therapy can be the option of the future. There are already some promising experiments in animals, like topical subretinal injection of BBS-containing adenovirus, which delivered the missing BBS gene and rescued rhodopsin mislocalization and preserved the function of the eyes in experimental mice [18, 19]. Another such experiment is the administration of a melanocortin receptor agonist that attenuated obesity in BBS knockout mice, probably activating leptin receptor signaling [20].

In May 2010, an interesting case was published in "Clinical Genetics" by Genuis & Lobo, describing a 21 months old girl with BBS, who underwent testing for biochemical deficiencies and in whom nutritional status correction was undertaken. Surprisingly, patient's signs and symptoms (deteriorated vision, obesity, behavior and mood disorders) subsequently resolved over the course of several months and she maintained the normal status until the publication time – that was 7 years old [21].

In the light of this paper, it is possible that the setback of our patient's disorders during the last two years (with the exception of the teratoma occurrence that we do not know if it is related to BBS) could be due to the change in her diet.

We consider our case presentation important not only because of the unique association of diseases but also because of the problems issued by the treatment of this patient. Apart from the possible surgical accidents and incidents, the risk of, even partial, ovarian removal, might have induced a premature menopause in a 21 years old patient with ovarian failure and under the risk of central hypogonadism, with all the emerging consequences at metabolic, osseous, cardiovascular and psychic implications.

We also emphasize the importance of genetic counseling, especially in families in which cases of Bardet–Biedl syndrome were described, as our case. In case of IVF (*in vitro* fertilization) along with other ovarian parameters' evaluation [22], pre-implantation genetic diagnostics are available in families where the genetic mutation is known [23].

Conclusions

It is, up to our knowledge, the first time that an association BBS–ovarian teratomas is reported. The clinical implications lead us to consider that periodic total abdominal and thoracic investigation (ultrasound, MRI), not only renal or cardiac, is necessary in order to detect tumor occurrence. Due to possible complications, surgical laparoscopic removal of the teratomas is the best treatment option, with the help of an experienced surgeon. Genetic counseling is of major importance in BBS, in order to reduce the disease's burden and take appropriate preventive actions.

Conflict of interests

The authors declare that they have no conflict of interests.

Acknowledgments

The authors are grateful to Dr Teodora Camelia Vlădescu from the Department of Pathology of the "St. Pantelimon" Emergency Hospital, Bucharest, Romania, for her valuable support regarding the histopathological images.

Author contribution

Irina Tica and Oana-Sorina Tica equally contributed to this article.

References

[1] M'hamdi O, Ouertani I, Maazoul F, Chaabouni-Bouhamed H. Prevalence of Bardet–Biedl syndrome in Tunisia. J Community Genet, 2011, 2(2):97–99.

[2] Hirano M, Satake W, Ihara K, Tsuge I, Kondo S, Saida K, Betsui H, Okubo K, Sakamoto H, Ueno S, Ikuno Y, Ishihara R, Iwahashi H, Ohishi M, Mano T, Yamashita T, Suzuki Y, Nakamura Y, Kusunoki S, Toda T. The first nationwide survey and genetic analyses of Bardet–Biedl syndrome in Japan. PLos One, 2015, 10(9):e0136317.

[3] Beales PL, Elcioglu N, Woolf AS, Parker D, Flinter FA. New criteria for improved diagnosis of Bardet–Biedl syndrome: results of a population survey. J Med Genet, 1999, 36(6): 437–446.

[4] Castro-Sánchez S, Álvarez-Satta M, Cortón M, Guillén E, Ayuso C, Valverde D. Exploring genotype-phenotype relationships in Bardet–Biedl syndrome families. J Med Genet, 2015, 52(8):503–513.

[5] Ece Solmaz A, Onay H, Atik T, Aykut A, Cerrah Gunes M, Ozalp Yuregir O, Bas VN, Hazan F, Kirbiyik O, Ozkinay F. Targeted multi-gene panel testing for the diagnosis of Bardet Biedl syndrome: identification of nine novel mutations across BBS1, BBS2, BBS4, BBS7, BBS9, BBS10 genes. Eur J Med Genet, 2015, 58(12):689–694.

[6] Forsythe E, Beales PL. Bardet–Biedl syndrome. Eur J Hum Genet, 2013, 21(1):8–13.

[7] Webb MP, Dicks EL, Green JS, Moore SJ, Warden GM, Gamberg JS, Davidson WS, Young TL, Parfrey PS. Autosomal recessive Bardet–Biedl syndrome: first-degree relatives have no predisposition to metabolic and renal disorders. Kidney Int, 2009, 76(2):215–223.

[8] Godinjak Z, Bilalović N, Idrizbegović E. Laparoscopic treatment of ovarian dermoid cysts is a safe procedure. Bosn J Basic Med Sci, 2011, 11(4):245–247.

[9] Bhat MT, Santhosh MC, Hegde HV, Rao RP. Anesthetic management of a child with Bardet–Biedl syndrome undergoing post-auricular dermoid excision. J Anaesthesiol Clin Pharmacol, 2014, 30(1):117–118.

[10] Beales PL, Reid HA, Griffiths MH, Maher ER, Flinter FA, Woolf AS. Renal cancer and malformations in relatives of patients with Bardet–Biedl syndrome. Nephrol Dial Transplant, 2000, 15(12):1977–1985.

[11] Leveno KJ, Alexander JM, Bloom SL, Casey BM, Dashe JS, Roberts SW, Sheffield JS (eds). Williams manual of pregnancy complications. 23rd edition, McGraw–Hill Professional, New York, 2012.

[12] Tica OS, Tica AA, Brailoiu CG, Cernea N, Tica VI. Sirenomelia after phenobarbital and carbamazepine therapy in pregnancy. Birth Defects Res A Clin Mol Teratol, 2013, 97(6):425–428.

[13] Dolan MS, Hill C, Valea FA. Benign gynecologic lesions. In: Lobo RA, Gershenson DM, Lentz GM, Valea FA (eds). Com-rehensive gynecology. 7th edition, Elsevier, Philadelphia, 2016, 413–414.

[14] Cocu M, Thorne C, Mătuşa R, Tica V, Florea C, Asandi S, Giaquinto C. Mother-to-child transmission of HIV infection in Romania: results from an education and prevention programme. AIDS Care, 2005, 17(1):76–84.

[15] Green JS, Parfrey PS, Harnett JD, Farid NR, Cramer BC, Johnson G, Heath O, McManamon PJ, O'Leary E, Pryse-Phillips W. The cardinal manifestations of Bardet–Biedl syndrome, a form of Laurence–Moon–Biedl syndrome. N Engl J Med, 1989, 321(15):1002–1009.

[16] Desai A, Jha O, Iyer V, Dada R, Kumar R, Tandon N. Reversible hypogonadism in Bardet–Biedl syndrome. Fertil Steril, 2009, 92(1):391.e13–391.e15.

[17] Peter AL, Houk CP. Puberty and its disorders. In: Lifshitz F (ed). Pediatric endocrinology. Vol. 2, Informa Healthcare, New York, 2007, 353–354.

[18] Simons DL, Boye SL, Hauswirth WW, Wu SM. Gene therapy prevents photoreceptor death and preserves retinal function in a Bardet–Biedl syndrome mouse model. Proc Natl Acad Sci U S A, 2011, 108(15):6276–6281.

[19] Seo S, Mullins RF, Dumitrescu AV, Bhattarai S, Gratie D, Wang K, Stone EM, Sheffield V, Drack AV. Subretinal gene therapy of mice with Bardet–Biedl syndrome type 1. Invest Ophthalmol Vis Sci, 2013, 54(9):6118–6132.

[20] Seo S, Guo DF, Bugge K, Morgan DA, Rahmouni K, Sheffield VC. Requirement of Bardet–Biedl syndrome proteins for leptin receptor signaling. Hum Mol Genet, 2009, 18(7): 1323–1331.

[21] Genuis SJ, Lobo RA. Potential amelioration of morbidity in patients with chromosomal anomalies: relevance to Bardet–Biedl syndrome. Clin Genet, 2011, 79(5):482–488.

[22] Tica VI, Mares P, Gouzes C, Badea P, Popescu G, Tica I. The variation of serum cortisol during ovarian stimulation for *in vitro* fertilization. Gynecol Endocrinol, 2008, 24(1):12–17.

[23] Pasińska M, Dudarewicz L, Jakubowski L, Haus O. Prenatal and postnatal diagnostics of a child with Bardet–Biedl syndrome: case study. J Mol Genet Med, 2015, 9(4):189.

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Received: March 10, 2016

Accepted: December 23, 2016