

Amenorrhea in Russell-Silver syndrome calls for an early gynecological intervention

Taranika Sarkar, Charles Allison

ABSTRACT

There has been considerable research on Russell-Silver Syndrome (RSS) which has an incidence of 1 in 30,000 to 1 in 100,000 people. Although numerous case reports have been published on children with RSS, very few have emphasized on adults. In this case report, we present a case of RSS in a 22-year-old women who presented with amenorrhea and abdominal pain. Normal menstrual cycle and normal estrogen level are necessary for bone health, lipid profile, cardiovascular health and mental health. An early intervention will thus help to reverse the effects of irregular menstrual cycles on long term health and address other causes like premature ovarian failure. The purpose of this report is to invite researchers to investigate whether there is a correlation between RSS and menstrual abnormalities, in which case early screening for ovarian and genital tract abnormalities in RSS will help to address the reproductive issues before a permanent consequence develops.

Keywords: Amenorrhea, Mayer-Rokitansky-Küster-Hauser, Russell-Silver syndrome

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INTRODUCTION

Russell-Silver Syndrome (RSS) as described by Silver et al. 1953 [1] is a genetic disorder characterized by low birth weight, post-natal short stature, characteristic facial feature and body asymmetry. RSS is one of the cause of Intrauterine Growth Restriction (IUGR) due to chromosomal abnormalities [2]. The features that distinguishes it from IUGR of other causes are feeding difficulties, body asymmetry and relative macrocephaly [3]. Three out of five cases reported by Russell [4] had imminent abortion, vaginal bleeding and abnormal placenta.

RSS most commonly involves chromosomes 7 and 11. Maternal uniparental disomy of chromosome 7 (5–10%) and hypomethylation of paternal imprinting region 1 (ICR-1), H19 due to imprinting error (22–65%) are the two most common mechanism of RSS [5]. Apart from these, two cases of balanced translocation and deletion involving chromosome 17 have also been reported by Hitchins et al. in 2001 [6]. The mode of inheritance has been suggested as autosomal recessive, autosomal dominant and X-linked in various studies [7–11].

The H19 Insulin-like Growth Factor (ICR) regulates Insulin-like Growth Factor 2 (IGF-2) and H19. Thus, hypomethylation results in overexpression of H19 and down-regulation of IGF-2. Serum IGF-2 levels are normal, whereas the levels of IGF-1 and IGF binding protein 3 are elevated in hypomethylated patients [12]. So this leads to growth restriction in RSS patients. It has also been studied by Ariel et al. that same H19 is responsible for differentiation of human female reproductive tract during menstrual cycle [13]. Also, a variety of ovarian cancers from germ cell to epithelial cancers has been attributed to the loss of imprinting of H19 and IGF-2 gene [14]. The degree of H19 hypomethylation has been associated with phenotypic severity and genital anomalies of RSS in both males and females [15].

Based on the above argument, in this paper, we claim that a correlation might exist between RSS and abnormalities in the female reproductive organs. Hence this necessitates an early gynecological referral for screening of reproductive abnormalities in female RSS patients. To support our claim we present a case of an adult female with RSS as described below.

CASE REPORT

A 22-year-old woman presented to our clinic with amenorrhea since last six months. She had her menarche at 19 years of age after she started taking combined oral contraceptive pills (COCP) for contraception. Even with COCPs, menstrual cycles were irregular, occurring roughly every four months. Bleeding was normal in amount. She was sexually active. She stopped hormone therapy one month ago for anxiety. Her pregnancy test was found to be negative. She had no vaginal discharge, no weight gain, no hirsutism, no cold intolerance, no galactorrhea, no headaches, no dysmenorrhea and no dyspareunia. The patient indicated that she exercises but not to the degree of causing amenorrhea. There was no family history of delayed menarche, irregular menstrual cycles, or constitutional pubertal delay. She denied use of steroid medications other than COCPs. She had no history of smoking.

The patient also complained of intermittent bloating and moderate pain in her abdomen since last three months. She developed these episodes particularly after consuming food. The pain was felt all over the abdomen with radiation to the back. There was no change in intensity with bowel movements; the intensity increased with activity. Severe constipation (with hard stools once a week) was noticed after she changed her diet to gluten-free diet. She tried laxatives without help and discontinued them. She noticed some weight loss in last two months. Amount could not be documented. She had no fecal urgency incontinence, no dyschezia, no hematochezia, and no vomiting. Since the pain started after amenorrhea there was no way to document whether it had any relation to menstrual cycles. She had no travel history in the recent past.

Physical examination revealed a lean female with triangular face and prominent forehead without an asymmetry or clinodactyly. Arching of feet was noticed. Breast examination was not done. No lymphadenopathy, thyromegaly, or pigmentation was noticed. Pelvic examination revealed a normal external genitalia with no vaginal discharge. No distension was found on abdominal examination. Auscultation resulted in normal bowel sounds. Mild diffuse tenderness without guarding rigidity or rebound was felt on deep palpation. No costovertebral angle tenderness (CVAT) or organomegaly was noticed. The patient did not have trigger points. Pregnancy test was negative again. USG abdomen revealed biliary sludge and right lower quadrant (RLQ) and left lower quadrant (LLQ) ascites (Figure 1).

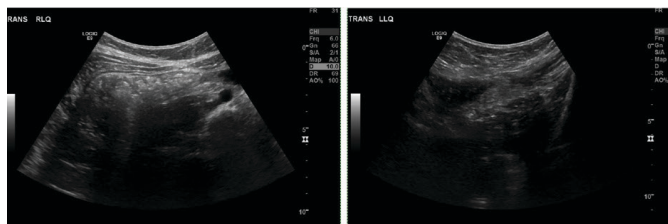


Figure 1: USG abdomen showed right and left lower quadrant ascites.

The patient appeared to have a flat affect. She was prescribed antidepressant, counselled to continue laxatives and change of diet back to high fibre gluten rich food. Hormonal therapy was also resumed. LFT (Liver function tests), TSH (Thyroid Stimulating Hormone) and prolactin levels were found to be within normal range. Pap smear finding was negative. Chlamydia and gonorrhoea testing was negative. Pelvic USG, LH (Luteinizing hormone), FSH (Follicle Stimulating Hormone), and testosterone were ordered but patient had not done it. She was counseled on the impact of her symptoms on her reproductive health and was advised to come for follow-up.

The patient was diagnosed with failure to thrive after birth. She had IUGR with feeding difficulties and had episodes of hypoglycemia. She was followed up by pediatric gastroenterologists for feeding therapy. Failure to catch up growth with dysmorphic facial features led to a work up and testing for genetic conditions. Finally a clinical diagnosis of RSS was given. She had short stature all throughout childhood and no pubertal growth spurt. Midparental height was within normal range, no history of familial short stature and constitutional delay. Bone age testing was not done. There was no spontaneous catch up-growth and height achievement ruled out constitutional delay. Further workup and genetic confirmation of RSS was done by uniparental disomy studies (UPD). Her growth hormone injection was started at eight years and continued till 14 years of age at a dose of 42 micrograms/kg/day. Her height was 4 feet 11 inches, not equal to her calculated target height. Menarche started at 19 years of age after she started taking oral contraceptive pills for contraception. History regarding breast development could not be given by the patient. The patient had recurrent emergency department visits due to hematuria. Kidney, ureter, and bladder (KUB) X-ray was normal. CT scan was negative for nephrolithiasis and gastrointestinal pathology and revealed ovarian cysts (Figure 2) and a relatively smaller uterus (Figures 2 and 3). Urinalysis showed no bacteria. HIDA scan was negative. The patient had a past history of kidney stones on the left side. Cognitive development was normal in her case and she completed her graduation studies recently.

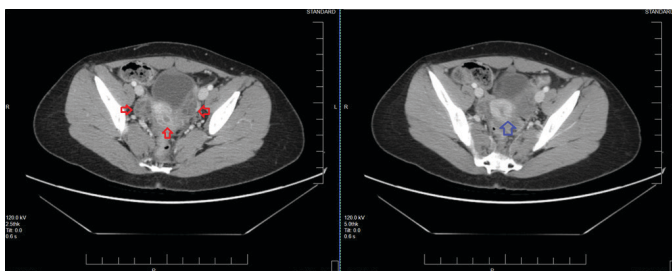


Figure 2: Computed tomography scan of pelvis (transverse section) shows multiple cysts in both the ovaries (red arrows) and relatively smaller uterus (blue arrow).

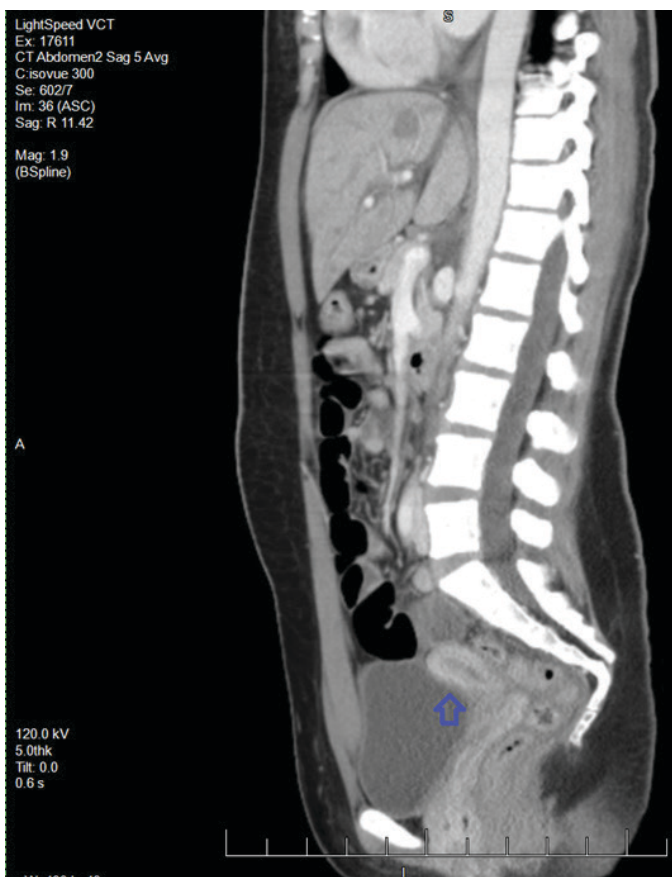


Figure 3: Computed tomography scan of abdomen (sagittal section) shows a relatively smaller uterus (blue arrow).

DISCUSSION

Male RSS patients have been reported to have various phenotypic features ranging from hypospadias, cryptorchidism, testicular agenesis, torsion, cancer in a number of studies [16]. Females on the other hand, mostly have normal menstrual cycles. However, Blik et al. [6, 16] and Price et al. [17] reported cases with uterine and vaginal anomalies. The co-occurrence of Mayer-Rokitansky-Küster-Hauser (MRKH) has been noted by Bellver et al. in some cases of RSS [18]. MRKH commonly presents with primary amenorrhea. The presentation of secondary amenorrhea with MRKH is rare but has been reported [19]. Representing possible cause of amenorrhea with RSS are given in Table 1.

Table 1: Representing possible cause of amenorrhea with RSS

Amenorrhea causes	Supporting evidence (in our patient)	Further investigation/ treatments needed
Mayer-Rokitansky-Kuster-Hauser (MRKH) syndrome	Recurrent hematuria without renal stones, normal external genitalia, delayed menarche induced with COCP, oligomenorrhea,	Pelvic Ultrasonography, MRI Treatment: surgical correction for pregnancy (if desired)
Ovarian insufficiency/ Premature Ovarian Failure (POF)	Delayed menarche induced with COCP, oligomenorrhea, pubertal growth delay, anxiety and depression	Serum (AMH, LH, FSH), Pelvic Ultrasonography, Treatment: Hormone Replacement Therapy (HRT), counseling for impact on fertility, oocyte donation (if pregnancy desired)
Ovarian tumors	Hormonal irregularities, abdominal pain, bloating and some weight loss	Pelvic ultrasonography, Treatment: Surgery and biopsy to rule out cancer
Polycystic Ovarian Syndrome (PCOS)	Oligomenorrhea, secondary amenorrhea	Pelvic ultrasonography, Serum LH, FSH, testosterone Treatment: Metformin, COCP, clomiphene citrate (if pregnancy desired)
Hypothalamic failure	Anxiety and depression	Serum LH, FSH, DHEAS, testosterone Treatment: Correcting the underlying issues

The patient in our case presented with delayed menarche induced by combined contraceptive pills (COCP), irregular menstruation and oligomenorrhea even with OCPs indicating a primary abnormality in menstrual regulation. Secondary amenorrhea developed later. Since renal abnormalities are associated with MRKH Type 2 [20], her recurrent hematuria without a diagnosis of renal stones might have been a result of MRKH. RSS can not only present with a typical MRKH but various degrees of abnormalities of the mullerian tract. Patients with mullerian anomaly usually have normal external genitalia and other secondary sexual characteristics, just like the patient in our case. Current ACOG (American College of Obstetricians and Gynecologists) guidelines highlight the need for examination of internal genitalia in patients with menstrual disorders younger than 21 year of age [21]. Early diagnosis is thus necessary for psychological counseling to make the patient understand the implications on reproduction.

Another possible cause of her amenorrhea might be ovarian insufficiency and premature ovarian failure. Ovarian insufficiency can result in mood swings and atrophic vaginitis. Our patient presented with a delayed menarche induced with COCP, oligomenorrhea, pubertal growth delay and more recently anxiety and depression that could be attributed to estrogen imbalance. Genetic disorders or IUGR can predispose to premature ovarian insufficiency. It has been shown in previous studies by de Bruin et al. [22] that ovarian insufficiency can result in IUGR due to reduced number of primordial follicles at birth in patients with IUGR. So it can be claimed that premature ovarian failure (POF) can occur in woman born with IUGR. It might result from chromosomal rearrangements and epigenetic translocations [11, 23].

Whether RSS can increase the risk of ovarian failure should be investigated further. Our claim is based on the following evidences:

- I. There was a report on a case of premature ovarian failure in RSS [24];
- II. The association between RSS and Sertoli cell dysfunction has already been established by [21], but such association in females is yet to be studied;
- III. Chromosomal translocations and deletions have been associated with infertility and spontaneous abortion; translocations and epigenetic alterations have been found by Burton et al. in many cases on POF [11, 23]. RSS is a spectrum of disease with different types of chromosomal rearrangements and epigenetic alterations and thus can lead to POF;
- IV. Patients reported first by Silver et al. [1] and later by Curi et al. [25] had elevated urinary gonadotropin;
- V. An uncommon finding of hypertrophic hypogonadism, and absence of ovaries in a RSS patient was described by Bliet et al. [17];
- VI. An RSS patient with ectopic localization of ovaries was reported by Bellver et al. [18];
- VII. RSS patients have delayed bone age. Bone age is delayed mostly in patients with hypothyroidism, growth hormone deficiency, and constitutional delay. According to Wakeling et al. [3], growth hormone levels are usually normal in RSS patients. Current research has shown that estrogen also regulates bone age [26] and hence estrogen imbalance can cause delayed bone age. Anti-mullerian hormone (AMH), LH and FSH are markers of ovarian insufficiency. Even though Goedegebuure et al. [27] have shown that levels of AMH, LH, and FSH were normal, the study was limited with a considerably small sample set. Conte et al. [28] have shown that levels of LH, FSH can be normal in POF in a specific age group (infancy to adolescence).

It is important to diagnose ovarian insufficiency and impending POF in young RSS patients. Like older women

estrogen deficiency results in low bone mineral density (BMD) in younger women [29] and increases the risk of non-traumatic femoral neck and wrist fracture. Our patient was taking [combined oral contraceptive pills (Yaz)], which has been found to be less effective than the more physiological hormone replacement therapy (HRT) in POF for adequate BMD [30].

Apart from the above, polycystic ovarian syndrome (PCOS) might also be responsible for her symptoms. PCOS is the most common cause of secondary amenorrhea. It has been found by Nestler et al. that hyperinsulinemia plays an important role in the pathogenesis of PCOS [31]. It might be an incidental finding but RSS may have increased risk of PCOS. Our claim is because of the following:

- I. RSS is shown to be associated with hyperinsulinemia [3, 18];
- AI. Growth hormone therapy that is used in RSS patients has also been known to cause insulin resistance and hyperinsulinemia [32];
- BI. IUGR, SGA have been shown by Hofman et al. to develop insulin resistance [33], and RSS causes IUGR.

Thus it is necessary to rule out PCOS and address any metabolic abnormality and irregular cycles to prevent endometrial cancer.

Amenorrhea can also result from functional ovarian tumors like sex cord stromal tumors. Ovarian tumors are commonly found to be associated with hormonal irregularities ranging from oligomenorrhea to polymenorrhea. In this study, our hypothesis is that RSS patients might be predisposed to ovarian neoplasm. Supporting evidences are:

- I. Genomic imprinting of human 11p15.5 has been involved in variety of malignancy [34];
- II. Hypomethylation of H19 was seen in human bladder cancer [35];
- III. Hypomethylation of H19/IGF2 was observed in ovarian teratoma [36];
- IV. There has been incidence of hepatocellular cancer [37], testicular cancer, craniopharyngioma, Wilms tumor [38], teratoma, and astrocytoma [37], and and ovarian choriocarcinoma [39–41] in RSS patients.

Our patient presented with abdominal pain, bloating and some weight loss with amenorrhea which could be explained by an ovarian growth.

Functional hypothalamic amenorrhea (FHA) might be another cause of amenorrhea in our patient. It results from severe weight loss, strenuous exercise, stress, anxiety and depression. These factors disturb the normal pulsatile GnRH release ultimately leading to hypoestrogenism. This is a reversible condition, but if left untreated can impact bone, mental, and cardiovascular health. Some of the patients even develop diabetes mellitus [42]. RSS patients might be predisposed to FHA because of:

- (a) FHA of adrenal origin. Early adrenarche has been reported by Binder et al. in patients with RSS [43]. High levels of adrenal androgens can result in precocious puberty in male children and hirsutism and ambiguous genitalia in female children. Whereas in adult females it can cause amenorrhea, oligomenorrhea, and hirsutism. High androgens suppress the hypothalamic pituitary axis, resulting in hypoenstrogonic state [44]. There has been cases of hirsutism of adrenal origin in RSS patients [18], ambiguous genitalia without an abnormal X/Y chromosome [45], and precocious puberty in RSS patients [46].
- (b) FHA due to psychosocial impact of RSS. It has been previously shown that RSS patients might develop symptoms of fatigue and pain [47]. Early diagnosis as a part of multi-disciplinary team can help these patients.

Our patient presented with anxiety and depression making FHA a possibility.

Finally, post pill amenorrhea may have been the cause after all of amenorrhea, but it is necessary to rule out other causes of menstrual abnormalities, especially with a background of a genetic disorder, delayed menarche, pubertal growth delay and oligomenorrhea.

CONCLUSION

From the above case study we conclude that pelvic ultrasonography, serum LH, FSH, testosterone, and early gynecological referral should be a part of a multidisciplinary team approach in female RSS patients presenting with any menstrual issues.

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Author Contributions

Taranika Sarkar – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Charles Allison – Acquisition of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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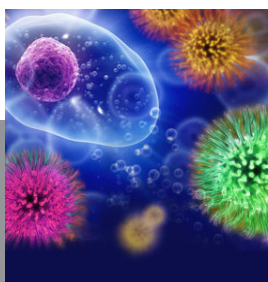
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