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Original Article

Ultrasonographic Changes of the Uterus and Ovaries in Female Infants with Congenital Adrenal Hyperplasia: Pseudo-Testicular Sign

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ABSTRACT

Background: Congenital Adrenal Hyperplasia (CAH) is one of the main causes of ambiguous genitalia. The unusual appearance of internal genitalia in CAH patients is similar to many other conditions which are classified in Disorders of Sex Development (DSD). This study aimed to accurately describe diagnostic ultrasonic features of the uterus and ovaries in CAH patients in order to distinguish it from other causes of ambiguous genitalia.

Methods: This cross-sectional study was performed in Akbar Children Hospital, Mashhad University of Medical Sciences, Mashhad, Iran, from 2017 to 2020. Ultrasound findings of the uterus and ovaries of 22 female infants (2-60 days of age) with CAH due to 21-hydroxylase deficiency and 47 healthy infants with a similar age were recorded and eventually analyzed in this study.

Results: All the healthy infants in the control group had a normal prominent cervix, except for two neonates (95%). In the case group, only 9 (41%) infants had a normal prominent cervix, and other 13 newborns had nearly equal sizes of fundus and cervix. There was a significant difference between the two groups in the fundus-to-cervix ratio (P=0.009). The 77% patients had no follicles in both ovaries, while 28% healthy infants in the control group had no follicles, and the rest had unilateral or bilateral multi-follicular ovaries. After two months following treatment, bilateral multi-follicular ovaries were observed in all patients. The sign of non-follicular ovaries (pseudo-testicular appearance) was significantly more prevalent in the case group (P=0.004). Furthermore, half of infants showed normal pelvic lymph node that mimic a testicular-like appearance due to its uniform hyper-echoic texture.

Conclusion: The testicular-like appearance of normal pelvic lymph nodes and non-follicular ovaries in a female infant with CAH. Attention to these usual findings can prevent misdiagnoses of cryptorchidism and time loss to perform other laboratory tests and karyotyping.

Keywords: Congenital adrenal hyperplasia, Disorders of sex development, Ovary, Ultrasound

Introduction

Ambiguous genitalia is a condition, which may be associated with many different medical disorders classified as Disorders of Sex Development (DSD). Early detection of the causative disorder permits correct gender assignment, reduces parental concerns, and provides an opportune time for the treatment to prevent life-threatening conditions, such as the adrenal crisis in Congenital Adrenal Hyperplasia (CAH). One of the most common causes of ambiguous genitalia in females is CAH, which is commonly developed due to an autosomal recessive heterogeneous genetic disorder leading to 21-hydroxylase deficiency, which impairs the biosynthesis of adrenal steroids (disorders of cortisol biosynthesis). More than 90% of CAH patients have a defect in the 21-hydroxylase enzyme. Infants and children with 21-hydroxylase deficiency have a different variation of symptoms corresponding to the level of enzymatic deficiency from severe salt-wasting

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forms to only simple virilizing disease (1).

The detection of CAH depends on careful history taking as well as accurate physical examination of infants with suspicious findings. Infants with indicative features, including ambiguous genitalia, salt wasting, and virilization are suspicious cases of CAH and will further undergo biochemical evaluation, imaging studies, and genetic testing if possible (2). The mortality rate of CAH will be declined if it is early diagnosed using recent advances in managing the adrenal crisis, followed by the implementation of adequate dosing of glucocorticoids (3). However, the CAH still has a substantial burden for both physicians and patients for gender assignment and abnormal external genitalia (4, 5).

Although evidence on the treatment of CAH is satisfactory, there is still a dearth of research describing diagnostic changes in neonates. In the current literature, except for few papers reporting the development of giant ovarian cysts in some cases, other changes in internal genitalia have not been described in female neonates with CAH (6). Furthermore, the ultrasound features of the uterus, ovaries, and detailed structure of ovarian follicles have not been addressed in CAH patients during infancy. Unusual appearance of internal genitalia in the CAH patients may simulate other causes of DSD, thereby delaying correct diagnosis. Accurate recognition of the features of the uterus and ovaries improves both diagnostic performance and differentiation from other causes of ambiguous genitalia.

Therefore, regarding the importance of early diagnosis of CAH, this study aimed to investigate ultrasound findings, especially, a detailed sonographic pattern of ovarian and uterine architecture in these patients for the first time.

Methods

This prospective cross-sectional study was performed in the Departments of Radiology and Endocrine, Akbar Children Hospital, Mashhad University of Medical Sciences, Mashhad, Iran from April 2017 to February 2020. The study protocol was approved by the Medical Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (IR.MUMS.MEDICAL.REC.1398.803).

All infants (age range: 2 days-2 months) suspicious of CAH (ambiguous genitalia, scrotal hypospadias, and virilization symptoms with or without salt wasting signs and symptoms) who were referred for a full abdominal and pelvic ultrasound examination, were evaluated for uterus, ovaries, and adrenal changes. The ultrasound machines included Esoate Class C or Samsung H60 with 5-12 MHz multi-frequency probes. Ultrasound examinations were performed by an expert pediatric radiologist in the sleeping or relaxing state with a semi-full bladder for good visualization of the pelvic cavity, uterus, and ovaries. It should be noted that it was impossible to visualize both ovaries performing light-graded compression ultrasound in all infants.

The clinical diagnosis of CAH was achieved with a physical examination, as well as laboratory and karyotype tests, ultrasound examination, or history of familial 21-hydroxylase deficiency. When the diagnosis was proven, the patients were followed-up for treatment effects. During two years of follow-up, 22 neonates and infants with a 46, XX karyotype who had 21-hydroxylase deficiency CAH were enrolled in the study. Furthermore, demographic, clinical, laboratory (e.g. 17-hydroxy progesterone, testosterone, and cortisol), and ultrasound findings were recorded for each patient. The analyzed ultrasound variables included uterus size, uterus to cervix ratio, ovaries echo, texture and size, existing follicles and/or cyst in ovaries, adrenal glands shape (cerebriform pattern), and bilateral symmetry (Figure 1).

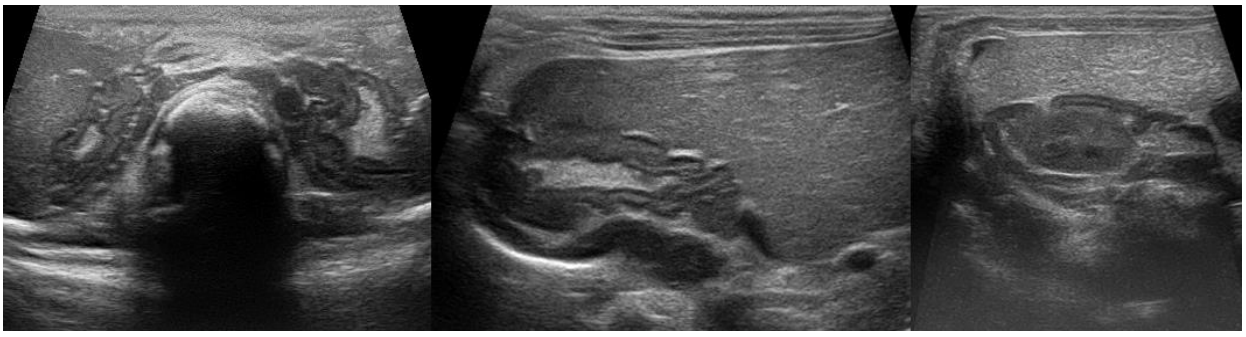

Figure 1. Ultrasonographic changes of adrenal glands in infants with Congenital Adrenal Hyperplasia: A) Bilateral cerebriform view of the enlarged adrenal gland. B and C) Before and after treatment views of right adrenal: decreased size and disappearing cerebriform pattern of the adrenal gland is obvious

Patients were managed under appropriate medical therapy with sufficient doses of corticosteroids and fludrocortisone if required. The second ultrasound exam was performed after a two-month course of treatment to evaluate the treatment response. The control group included 47 healthy neonates, and they were similar to the case group regarding age; moreover, their ultrasound variables were studied in the same manner. The data were analyzed in SPSS software (version 16).

Results

This study included 22 female neonates with CAH and a mean age of 23.3 (3-60) days and 47 normal neonates with a mean age of 29.3 (5-62) days. All patients with CAH had subjective adrenal enlargement and cerebriform appearance. Moreover, 86% and 14% of them were bilateral and unilateral, respectively (left side).

Furthermore, 13 cases of the patient group had nearly equal fundus and cervix size, and 9 (41%) neonates had a prominent cervix. On the other hand, all normal neonates had a prominent cervix, except for two cases (Figure 2). A significant difference was observed between the two groups in the fundus-to-cervix ratio (P=0.009). However, regarding the uterus size, the mean values were estimated at 32.2±5.7 and 31±8 mm in the case and control groups, respectively, with no significant difference between them in this regard (P=0.96). Additionally, the mean ovarian sizes (the largest dimension) were estimated at 10.7±5.8 and 14.1±6.4 mm in the case and control groups, respectively, which was significantly larger in the control group (P=0.016).

Evaluation of ovarian echogenicity revealed that non-follicular ovaries are iso-echoic, compared to the uterus; however, when follicles appear, they become hypoechoic. Ovarian follicular visibility was evaluated in the case and control groups, and the results showed that in the case group, 17 (77%) neonates did not have any visible follicles in both ovaries (Figure 3). Moreover, 3 (18%) and 2 (9%)

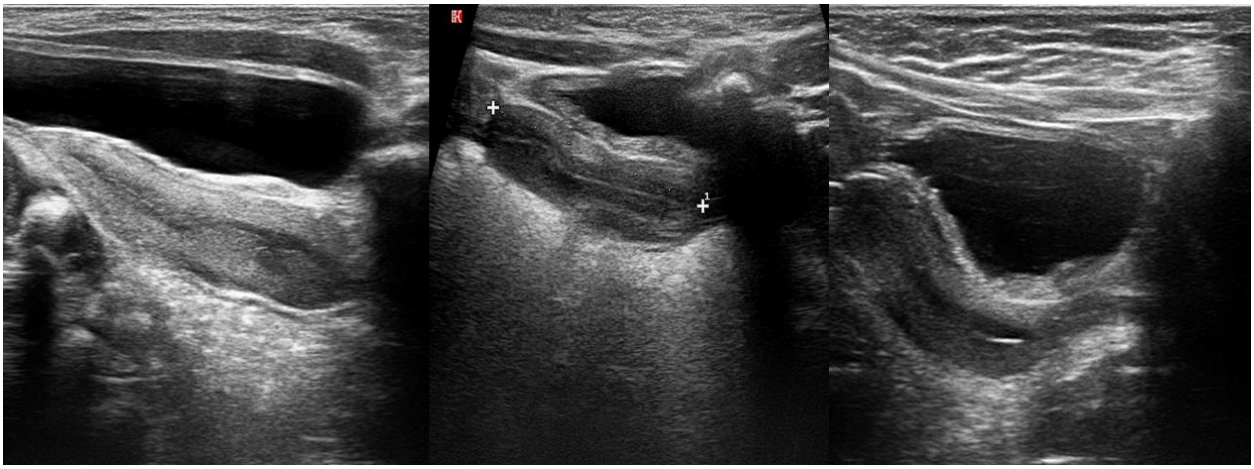

Figure 2. Ultrasonographic views of the uterus in infants with Congenital Adrenal Hyperplasia: fundus completely larger than cervix, fundocervical ratio > 2 (A), fundus slightly larger than cervix, fundocervical ratio < 2 (B), and fundus size equal to the cervix (C)

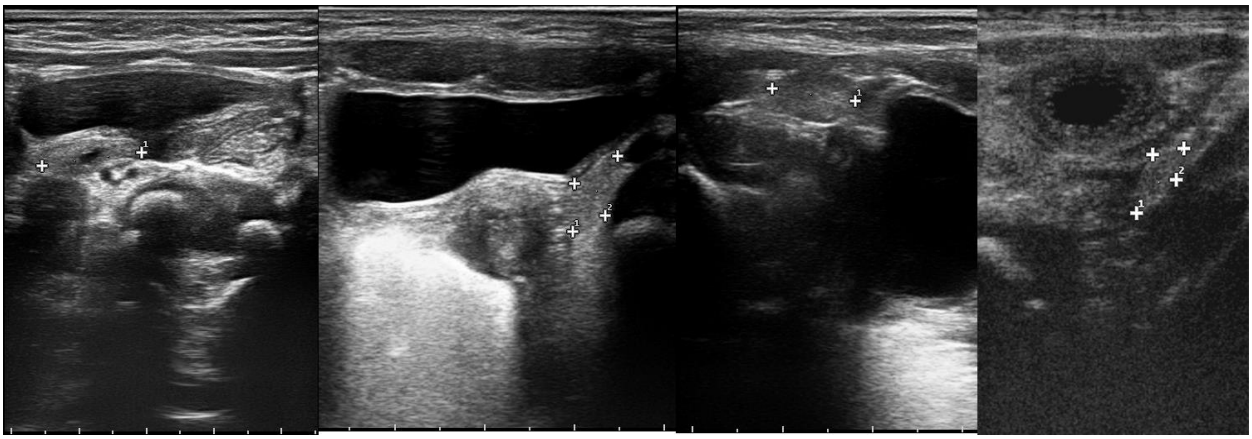

Figure 3. Pseudo-testicular pattern of ovaries in several infants with Congenital Adrenal Hyperplasia

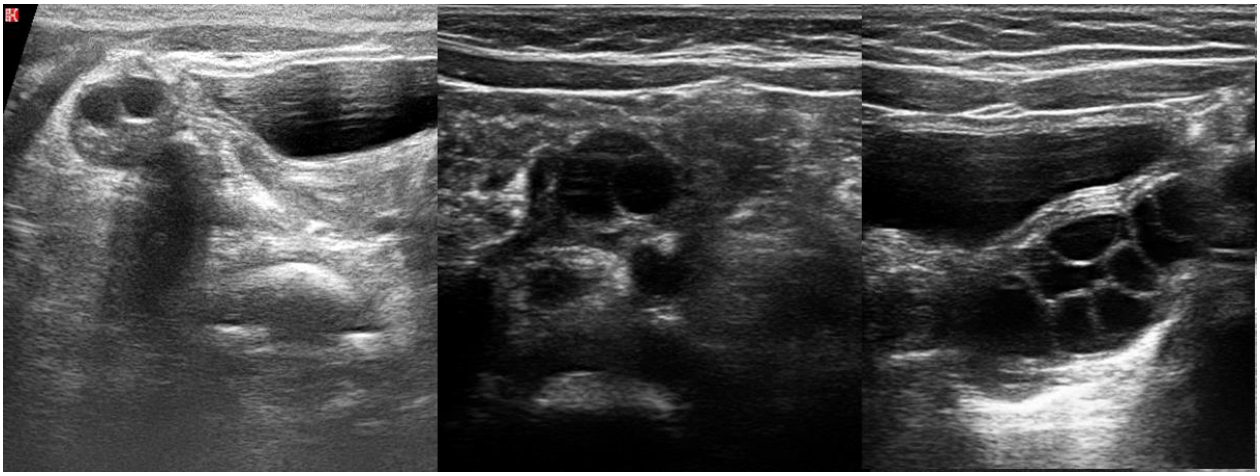

Figure 4. Normal follicles appearing after treatment in several cases

cases had few unilateral small follicles and bilateral multi-follicular ovaries, respectively. On the other hand, 13 (28%) neonates had no follicles in their ovaries in the control group. However, 9 (19%) and 25 (53%) newborns had unilateral follicles and bilateral multi-follicular ovaries, respectively. Non-follicular ovaries (pseudo-testicular appearance) were significantly more prevalent in the case group, compared to the control group (P=0.004).

In the second ultrasound examination after two months of treatment, bilateral multi-follicular ovary (Figure 4) was observed in all patients, and cerebriform adrenal enlargement disappeared in all patients, except for one case. A normal lymph node around the external iliac vessel was observed in half infants unilaterally or bilaterally. These lymph nodes had a uniform hyper-echoic texture with or without poor cortico-medullary differentiation and with a testicular-like pattern (Figure 5). In addition, they were commonly observed between the caudal part of the external iliac vessels and the abdominal wall.

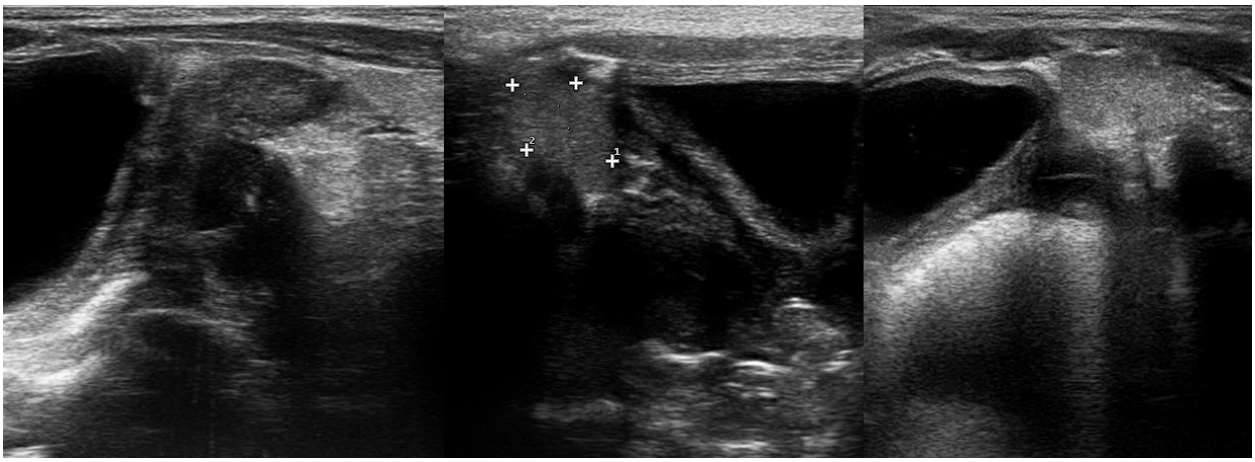

Figure 5. Pseudo-testicular pattern of normal lymph nodes, which are characteristically located between external iliac vessels and abdominal wall

Discussion

In the majority of the patients with ambiguous genitalia, the appearance of the external genitalia cannot lead to gender assignment immediately after birth and detection of the etiologic background without imaging assistance. Gender assignment is necessary to select an appropriate management plan and identify the nature of the disorder. Although both Computed Tomography and Magnetic Resonance Imaging are available for the evaluation of adrenal pathology, ultrasound study is widely used in children. To date, published ultrasound studies in the neonatal period are mostly summarized in evaluating the adrenal glands (enlarged cerebriform adrenal) as

well as describing the vaginal anatomy in girls with CAH (2,7). In our study, all the patients had obvious bilateral or unilateral characteristic cerebriform adrenal enlargements. Therefore, it is proposed that adrenal size measurement is not required in these patients.

The detailed structures of the uterus and ovaries during the infancy of CAH patients have not yet been well explained. In the infancy period, due to exposure to maternal and placental hormones, the Follicle-Stimulating Hormone is a dominant hormone in the postnatal period and stimulates ovarian follicular maturation. This results in relatively large size of the neonatal uterus and ovaries, compared to their size later. In addition, the ovarian follicles are observed in many normal neonates in ultrasound examinations (8, 9). In total, 78% of our healthy cases had unilateral or bilateral multi-follicular ovaries; moreover, all healthy cases, except for one neonate, had a normal prominent cervix.

The results of the present study showed that hormonal disturbance could affect the fundus-to-cervix ratio in CAH infants. Although there was no significant difference between the two groups in terms of the uterus size (P=0.96), impairment in the fundus-to-cervix ratio was observed in the neonates and infants with CAH. Totally, 56% and 44% of patients had nearly equal fundus and cervix sizes, as well as the normal prominent cervix, respectively.

It has been previously noted that young cases of CAH who experience a hyper-androgenic state during their development are more prone to ovarian hyperandrogenism (10). An abnormal steroidogenic activity leads to elevated androgen level in the ovary that is associated with follicle maturation arrest. This mechanism is the cause of anovulation in polycystic ovary syndrome patients (11). It has been reported that approximately 3% of pre-and peri-pubertal females with CAH have polycystic ovaries, and this value increases as the patients grow (12). In addition, the development of ovarian cysts has been reported in some neonates with CAH that were treated by glucocorticoids. The elevated level of androgen stimulates the formation of immature follicles, and therefore, may leads to ovarian cyst in some CAH patients (6).

However, in the present study, non-follicular ovaries (pseudo-testicular appearance) were significantly more prevalent in the case group, compared to the control group (P=0.004); moreover, in most CAH patients (87.5%), no follicle was detected in one or both of the ovaries. In addition, ovarian cysts were not observed in any of the patients. Developmental arrest of ovarian follicles during infancy is responsible for the pseudo-testicular appearance of the ovaries in CAH patients, and it may justify a significant decrease in the mean ovarian size in the case group, compared to the control group (P=0.016). This condition in the CAH patients is contrary to that in pre-pubertal age in which ovaries may have a polycystic appearance.

Nonetheless, early treatment of CAH can protect ovarian function (9). In our study, the second ultrasound findings after two months of treatment showed normal bilateral multi-follicular ovaries in all patients who had come back. The pseudo-testicular appearance of ovaries in a female infant with CAH gave a misleading picture to the diagnosis of a male infant with severe perineo-scrotal hypospadias and/or testicular feminization (androgen insensitivity syndrome). In addition, the presence of normal lymph nodes around the external iliac arteries may resemble the testicular appearance due to their uniform hyper-echoic texture with no or poor cortico-medullary differentiation. Careful attention to the location of these nodes, which are commonly located between the external iliac vessels and abdominal wall, is the key differential finding. Attention to the cerebriform appearance of adrenal glands and the existence of the uterus can differentiate between these conditions.

Although ultrasound examination of infants for CAH requires an asleep or relaxing state, and the detection of non-follicular ovaries as an auxiliary sign may seem to be time-wasting, it should be bear in mind that it can be a valuable modality to initiate the treatment as soon as possible to prevent salt-wasting crises. The other etiologies of androgen hypersecretion in children, such as adrenal tumors (adenomas, carcinomas), Cushing's syndrome, Glucocorticoid resistance, exogenous androgens, anabolic steroids, and placental aromatase deficiency, may have a follicular suppressive effect on ovaries simulating the appearance of CAH. Accordingly, further studies are required to be conducted on these etiologies. Additionally, the ultrasound appearance of internal genitalia in patients with sex chromosome mosaicism, true hermaphroditism, Turner syndrome, or mixed gonadal dysgenesis may simulate the same pattern, and further studies are helpful in this regard. Considering different aspects of other causes of DSD, studies with larger sample sizes of the patients are encouraged to be performed in near future.

Conclusion

Exposure to maternal and placental hormones (Follicle-Stimulating Hormone) in healthy infant stimulates ovarian follicular maturation and leads to a multi-follicular pattern of ovaries. The results obtained from our study on patients with CAH showed that the elevated androgen level was associated with an arrest in follicle maturation. This arrest is responsible for the pseudo-testicular appearance of the non-follicular ovaries in CAH patients during infancy which may lead to the misdiagnosis of cryptorchidism and other causes of ambiguous genitalia. Furthermore, our data also revealed that normal lymph nodes around the external iliac arteries might resemble the testicular appearance due to their uniform hyper-echoic texture. Therefore, the testicular-like appearance of pelvic lymph nodes is also an usual finding in a female infant with -hydroxylase deficiency. These two are usual findings in CAH patients and them should not be led to the misdiagnosis of other causes of ambiguous genitalia and losing the time to perform other laboratory tests and karyotyping. The cerebriform appearance of adrenal glands with the existence of the uterus is sufficient for the diagnosis of a female with CAH.

Acknowledgments

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Conflicts of interest

The authors declare that they have no conflicts regarding the publication of the study.

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