Case Report ISSN 2639-9342

Gynecology & Reproductive Health

Non-Classic Congenital Adrenal Hyperplasia Related to 3 Beta-Hydroxysteroid Dehydrogenase Deficiency Causing Premature Pubarche

Diane Check L[1], Jerome Check H[1,2,*] and Michael Dougherty P[3]

[1]*Cooper Institute for Reproductive Hormonal Disorders, P.C., MT. Laurel, NJ, USA.*

[2]*Cooper Medical School of Rowan University, Dept. Ob/Gyn, Div. Repro. Endo. & Infertility, Camden, NJ, USA.*

[3]*Medical College of Georgia, Reproductive Endocrinology, fertility, and Genetics, Augusta, Georgia, USA.*

***Correspondence:**
Jerome H. Check, M.D., Ph.D., 7447 Old York Road, Melrose Park, PA 19027, TEL: 215-635-4400; Fax: 215-635-2304.

Received: 17 January 2020; **Accepted:** 08 February 2020

Citation: Diane Check L, Jerome Check H, Michael Dougherty P. Non-Classic Congenital Adrenal Hyperplasia Related to 3 Beta-Hydroxysteroid Dehydrogenase Deficiency Causing Premature Pubarche. Gynecol Reprod Health. 2020; 4(1): 1-4.

ABSTRACT

Congenital adrenal hyperplasia (CAH) may be an etiologic factor for premature pubarche in about 12% of the cases, with the 21-hydroxylase deficiency as the most likely cause. A 4 ½ year old girl presented with premature pubarche and shortly thereafter developed severe chronic vulvovaginitis. She was suspicious as having a form of CAH since her brother also had premature pubarche. Though her androgens were elevated (i.e., testosterone and dehydroepiandrosterone sulfate as was her brother's) both of them had low 17-hydroxyprogesterone levels ruling out the non-classic 21 hydroxylase deficiency and neither were hypertensive ruling out the 11-beta hydroxylase deficiency. A serum 17-hydroxypregnenalone level could not be obtained on the female sibling because she was taking prednisone for asthma, but one could be obtained on the male. Indeed the 17-hydroxypregnenalone level was increased suggesting that they had the very rare form of non-classic CAH, the type II 3-hydroxysteroid dehydrogenase deficiency. The question now was how to treat her rare severe vulvovaginitis. Since her mother had manifestation of the increased cellular permeability syndrome with pelvic pain, headaches, and chronic fatigue and was successfully treated with dextroamphetamine sulfate, the female sibling was also treated with dextroamphetamine sulfate. Not only did her vulvovaginitis quickly disappear, but she showed marked improvement in her attention deficit disorder (ADD) and edema causing weight gain. Similarly, her brother showed significant improvement in his fatigue, weight gain and ADD. Her mother did not have premature pubarche, and thus the results suggest that though one may think that two rare conditions, i.e., premature pubarche and pediatric vulvovaginitis, occurring in the same patient may have a common etiology, the authors conclude that they are probably independent conditions.

Keywords

3 Beta hydroxysteroid dehydrogenase deficiency, Congenital adrenal hyperplasia, Increased cellular permeability syndrome, Premature pubarche, Vulvovaginitis.

Introduction

The non-salt-losing form of congenital adrenal hyperplasia (CAH), related to a 3 beta-hydroxysteroid dehydrogenase deficiency, has been found to be a rare cause of premature pubarche (defined as premature development of pubic hair before age 8 in girls and 9 in boys) [1,2]. The prevalence of premature pubarche in 4-8 years old girls was found in one study to be 4.3% [3].

The etiology of premature pubarche could include true precocious puberty, associated with thelarche and early menses, congenital adrenal hyperplasia, exogenous androgen exposure, androgen secreting tumors, and "idiopathic" premature pubarche [4]. The non-classic, non-salt losing, forms of CAH can present in adolescents and young women with androgen excess symptoms, e.g., hirsutism, acne, and male type sebaceous secretion with body odor.

By far, the most common form of adult onset CAH is associated with the 21 hydroxylase deficiency, and a distant second is the 11 beta hydroxylase deficiency, and even more rare is the type II 3 beta hydroxysteroid dehydrogenase deficiency. A slightly worse form of CAH can present with premature pubarche [5-7]. It is not clear as to what percentage of cases of premature pubarche have a form of non-classic CAH as the cause, since hormonal testing, even with stimulation, can have overlapping values with normal

children. Possibly, in the near future, a larger series of children with premature pubarche will be evaluated by using genetic testing for the CYP21A2 gene encoding for the 21-hydroxylase enzyme, or the CYP11B1 gene encoding for the 11 beta hydroxylase enzyme, of the HSD3B2 gene encoding for the type II 3 beta hydroxysteroid dehydrogenase enzyme. Then the true frequency of all types of CAH as a cause of premature pubarche could be determined and then what percentage of CAH causing premature pubarche has the type II 3 beta hydroxysteroid dehydrogenase deficiency as the etiologic factor for precocious puberty [8,9]. One estimate, based on genetic testing, is that CAH is present in 12% of cases of premature pubarche [10].

Pre-pubertal vulvovaginitis was not listed as an associated phenotypic symptom in pre-pubertal girls with early pubarche of various etiologies or specifically related to the 3 beta hydroxysteroid dehydrogenase type of CAH [1,2,10]. At the time of this publication, there has been only one case in the literature where severe vulvovaginitis was identified in a pediatric patient with premature pubarche [11]. The cause of the premature pubarche was unknown [11]. The present update in this case will provide evidence that the cause of the premature pubarche was the very rare non-classic type II 3 beta hydroxysteroid dehydrogenase deficiency type of CAH. However, based on the specific type of treatment, that completely eradicated the vulvovaginitis problem, up to her present age of 17.5 years, we conclude that the vulvovaginitis was unrelated to hormonal events causing premature pubarche [11].

Case Report

A 4.5 years old girl started to develop pubic and axillary hair and an adult male body odor. Adrenarche slowly progressed, and she had an adult type escutcheon by age 7. At age 5.5 she developed a malodorous vaginal discharge associated with severe labial burning pain, and loss of hair on her head.

In addition to her vulvovaginitis, she presented with other symptoms, e.g., sudden weight gain (had been thin before), changed from an academically top student to someone who more often than not was confused, and she was finding academics challenging.

The normotensive young girl was evaluated by many pediatric gynecologists, pediatric endocrinologists and infectious disease specialists, but no diagnosis was made. She had frequent testing for anemia, vitamin D deficiency, and for non-classic 21 hydroxylase deficiency, but on many occasions, her serum 17 hydroxyprogesterone levels were low-normal (<40 ng/dL). At age 6, her serum DHEA-s hormone was mildly elevated at 115 mcg/dL (normal <34 mcg/dL) with a slightly low 8:00a.m. cortisol of 7.8 mcg/dL (normal 9-22 mcg/dL). Her serum testosterone was slightly elevated for her age group at 8.1 ng/dL.

Premature puberty was excluded by measuring serum estradiol, LH, and FSH levels all being in the low range. She sought our advice on treating her vulvovaginitis at age 8.5. We considered that her vulvovaginitis may be related to the increased cellular permeability syndrome, where, related to inadequate dopamine secretion from sympathetic nerve fibers, there is infiltration of toxic agents causing inflammation and subsequent pain, not just in the pelvis, but in other tissues as well [12-18]. Indeed, her severe vulvovaginitis was completely abrogated following treatment with dextroamphetamine sulfate, which releases more dopamine from sympathetic nerve fibers.

Subsequent to her successful therapy with dextroamphetamine sulfate, not only for her vulvovaginitis, but for her unexplained weight gain, fatigue, mental confusion, and lack of focus (attention deficit disorder may be a manifestation of the increased cellular permeability syndrome as is fluid retention causing weight gain and fatigue), we learned that her younger brother started to develop pubic hair at the age of 6 [12,13,19,20]. This made us suspicious that she had some form of CAH as the etiologic factor for the premature pubarche. Actually, her mother asked if we would be willing to evaluate her 9 years old son, who not only had premature pubarche at age 6, but also had similar symptoms as her sister, i.e., weight gain, confusion and chronic fatigue. As with his sister, all of these symptoms (except the premature pubarche) similarly. markedly improved following treatment with dextroamphetamine sulfate.

Initially, when his sister presented, she had been taking prednisone for asthma preventing our group from performing hormonal studies, especially those related to CAH. However, the male sibling was not taking any exogenous glucocorticoids. Sera for a.m. cortisol, DHEA-s, 17-OH progesterone, and 17-hydroxypregnenolone, and 11-deoxycortisol were ordered. His 8:00a.m. serum cortisol was low normal at 9 mcg/dL (normal 9-22 mcg/dL). However, his 17-OH pregnenolone was increased at 247 mcg/dL (normal <188 mcg/dL). The lab unfortunately did not measure the serum 11-deoxycortisol level, but in view of the fact that both he and his sister were normotensive, we did not think it was necessary to obtain another serum sample for this test.

The female sibling is now age 17. Her menarche was at age 13 and thelarche at age 12. She is 62 inches tall and weighs 110.6 pounds. Her most recent blood pressure was 102/70 mg/Hg. A serum anti-mullerian hormone level was 3.92 ng/mL which was not elevated. She has no hirsutism or acne. She takes 20mg hydrocortisone in the morning and 10mg at 4:00p.m. Her attention deficit deficiency is reasonably well controlled and she remains a good student. Her recent total testosterone measured 5.1 ng/dL (normal <.25 – 39.8 ng/dL). She ingests 40mg amphetamine salts immediate release tablets each morning and 20mg at noon (a total of 37.6 mg dextroamphetamine sulfate). She has not had one episode of vulvovaginitis since her dextroamphetamine treatment began at age 8.5 (it had been present daily and severe for 2.5 years before treatment).

The male sibling is now 14.5 years old. Puberty began at age 13. He is treated with the same dosage of hydrocortisone and dextroamphetamine sulfate as his siter. He also takes 120mg of armour thyroid extract. He is 66 inches tall and weighs 100 pounds. His present blood pressure is 108/64 and has not had a problem

with acne. He recently ran out of his dextroamphetamine sulfate, and immediately he became severely fatigued and was mentally confused, and developed fibromyalgia symptoms. These all dissipated with restoration of dextroamphetamine sulfate therapy.

Discussion

One may have thought that since pediatric vulvovaginitis is unusual, that it may have been related somehow to her premature pubarche, which in turn, was probably caused by a rare 3 beta hydroxysteroid dehydrogenase deficiency. However, a search of the literature did not find any association of these two conditions. Furthermore, we have treated hundreds of patients with the increased cellular permeability syndrome, and these are the only two patients with a history of premature pubarche.

The siblings' mother was plagued by severe dysmenorrhea, chronic fatigue, and headaches, but did not have premature pubarche (nor did the father). She also responded very well to dextroamphetamine sulfate treatment. Thus, we believe that the premature pubarche was merely fortuitous and played no etiologic role in the vulvovaginitis. The vulvovaginitis would seem to be related to the increased cellular permeability syndrome, a condition that seems to have a polygenetic inheritance pattern, and probably came from the mother [13].

The increased cellular permeability syndrome is a common, but not well known, entity related to increased cellular permeability of certain tissues complicated by sympathetic nervous system hypofunction [12,13,21]. Sympathomimetic amine therapy has been demonstrated to improve all the symptoms of the mother and children including dysmenorrhea, vulvovaginitis, headaches, chronic fatigue, fibromyalgia, and weight gain related to fluid retention [19,20,22-24]. As mentioned, dextroamphetamine sulfate may stimulate the release of increased dopamine from the sympathetic nerve fibers, which may correct the cellular permeability defect [13].

We would have liked to obtain tests in the two siblings for the HSD3B2 gene mutation to confirm the diagnosis of the type II 3 beta hydroxysteroid dehydrogenase enzyme deficiency type of CAH as the cause of their premature pubarche, but insurance denied payment. The tests were otherwise cost prohibitive, and the results would not change management [25,26].

Though polycystic ovarian syndrome can sometimes present with premature pubarche, or adrenarche, this is not likely in the female patient since she exhibits no features of PCOS at age 17 [27]. Her serum AMH was not elevated, and her mother has no PCOS features [27]. Though some cases of the more common type of 21 hydroxylase type of CAH as the cause of premature puberty can only be established hormonally (i.e., without specific genetic tests), by measurement of 17-OH progesterone, not just at baseline, but after cosyntropin stimulation, this would not very likely be abnormal, in view of their low normal basal 17-OH progesterone levels [4]. An increase in 17-hydroxypregnenalone levels in the male sibling, with low normal levels of 17-hydroxyprogesterone, best fits with the very rare non-classic 3 beta hydroxysteroid dehydrogenase enzyme deficiency type of CAH as the etiologic factor of their premature pubarche in the presence of the common, but relatively, unknown condition of the increased cellular permeability syndrome as the cause of pediatric vulvovaginitis [7,11].

References

1. Pang S. The molecular and clinical spectrum of 3β-hydroxysteroid dehydrogenase deficiency disorder. Trends Endocrinol Metab. 1998; 9: 82-86.
2. Bongiovanni AM. The adrenogenital syndrome with deficiency of 3β-hydroxysteroid dehydrogenase. J Clin Invest. 1962; 41: 2086-2092.
3. Atay Z, Turan S, Guran T, et al. The prevalence and risk factors of premature thelarche and pubarche in 4- to 8-year-old girls. Acta Paediatr. 2012; 101: e71-e75.
4. Novello L, Speiser PW. Premature adrenarche. Pediatr Ann. 2018; 47: e7-e11.
5. Trapp CM, Oberfield SE. Recommendations for treatment of nonclassic congenital adrenal hyperplasia (NCCAH): an update. Steroids. 2012; 77: 342-346.
6. Wang D, Wang J, Tong T, et al. Non-classical 11β-hydroxylase deficiency caused by compound heterozygous mutations: a case study and literature review. J Ovarian Res. 2018; 11: 82.
7. Mermejo LM, Elias LLK, Marui S, et al. Refining hormonal diagnosis of type II 3β-hydroxysteroid dehydrogenase deficiency in patients with premature pubarche and hirsutism based on HSD3B2 genotyping. J Clin Endocrinol Metab. 2005; 90: 1287-1293.
8. Simard J, Rheaume E, Sanchez R, et al. Molecular basis of congenital adrenal hyperplasia due to 3β-hydroxysteroid dehydrogenase deficiency. Mol Endocrinol. 1993; 7: 716-728.
9. Temeck JW, Pang S, Nelson C, et al. Genetic defects of steroidogenesis in premature pubarche. J Clin Endocrinol Metab. 1987; 64: 609-617.
10. Oberfield SE, Sopher AB, Gerken AT. Approach to the girl with early onset of public hair. J Clin Endocrinol Metab. 2011; 96: 1610-1622.
11. Check JH, Cohen R. Marked improvement of vulvovaginitis of unknown origin in a pediatric patient – case report. Clin Exp Obst Gyn. 2014; 41: 723-724.
12. Check JH. Sympathomimetic amines are a safe, highly effective therapy for several female chronic disorders that do not respond well to conventional therapy. Clin Exp Obst Gyn. 2015; 42: 267-278.
13. Check JH. Changing the name of a syndrome: Sympathetic neural hyperalgesia edema syndrome becomes - the increased cellular permeability syndrome. Clin Exp Obst Gyn. 2017; 44: 819-823.
14. Check JH, Wilson C. Dramatic relief of chronic pelvic pain with treatment with sympathomimetic amines - case report. Clin Exp Obstet Gynecol. 2007; 34: 55-56.
15. Check JH, Cohen R. Chronic pelvic pain - traditional and novel therapies: Part II medical therapy. Clin Exp Obst Gyn. 2011; 38: 113-118.

16. Check JH, Cohen R. The triad of luteal phase ocular migraines, interstitial cystitis, and dyspareunia as a result of sympathetic nervous system hypofunction. Clin Exp Obst Gyn. 2014; 41: 575-577.
17. Check JH, Jaffe A. Resolution of pelvic pain related to adenomyosis following treatment with dextroamphetamine sulfate. Clin Exp Obstet Gynecol. 2015; 42: 671-672.
18. Check JH. Increased tissue permeability and sympathetic nervous system hypofunction may be the common link between dysmenorrhea, chronic pelvic pain, Mittelschmerz, and Crohn's disease. Clin Exp Obst Gynecol. 2016; 43: 112-113.
19. Check JH, Shanis BS, Shapse D, et al. A randomized comparison of the effect of two diuretics, a converting enzyme inhibitor, and a sympathomimetic amine on weight loss in diet-refractory patients. Endoc Pract. 1995; 1: 323-326.
20. Check JH, Cohen R. Sympathetic neural hyperalgesia edema syndrome, a frequent cause of pelvic pain in women, mistaken for Lyme disease with chronic fatigue. Clin Exp Obst Gyn. 2011; 38: 412-413.
21. Check JH, Cohen R, Katsoff B, et al. Hypofunction of the sympathetic nervous system is an etiologic factor for a wide variety of chronic treatment-refractory pathologic disorders which all respond to therapy with sympathomimetic amines. Med Hypoth. 2011; 77: 717-725.
22. Check JH, Check D, Cohen R. Sympathomimetic amine therapy may markedly improve treatment resistant headaches related to a vascular permeability defect common in women. Clin Exp Obst Gyn. 2009; 36: 189-191.
23. Check JH, Cohen R, Check D. Evidence that migraine headaches in women may be related to a common defect in the sympathetic nervous system as evidenced by marked improvement following treatment with sympathomimetic amines. Clin Exp Obst Gyn. 2011; 38: 180-181.
24. Check JH, Cohen R. Marked improvement of pain from long term fibromyalgia with dextroamphetamine sulfate in a woman who failed to improve with conventional pharmacologic treatment. Clin Exp Obst Gyn. 2014; 41: 90-92.
25. Oberfield SE, Tao RH, Witchell SF. Present knowledge on the etiology and treatment of adrenarche. Pediatr Endocrinol Rev. 2018; 15: 244-254.
26. Carmina E, Dewailly D, Escobar-Morreale HF, et al. Non-classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency revisited: an update with a special focus on adolescent and adult women. Hum Reprod Update. 2017; 23: 580-599.
27. Efthymiadou A, Bogiatzidou M, Kritikou D, et al. Anti-mullerian hormone in girls with premature adrenarche: The impact of polycystic ovary syndrome history in their mothers. J Pediatr. 2019; 205: 190-194.