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Isolated Absent Thelarche in a Patient With Neurofibromatosis Type 1 and Acromegaly

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Abstract

Background—Isolated absent thelarche is a rare condition that is infrequently reviewed in the literature.

Case—A 28-year-old woman with neurofibromatosis type 1 and acromegaly presented with absent breast development despite hormone therapy. Examination noted a normally developed female with acromegalic features and Tanner Stage I breasts. Hormone studies and karyotype were normal. Magnetic resonance imaging of the patient's brain demonstrated a voluminous pituitary. Chromosome microarray analysis diagnosed the NF1 microdeletion syndrome. Breast ultrasound and surgical consultation were offered.

Conclusions—Neither neurofibromatosis type 1, acromegaly nor the NF1 microdeletion syndrome are linked to absent thelarche. After attempting hormone therapy, patients with absent thelarche should be evaluated for congenital breast anomalies, estrogen receptor abnormalities or gene defects. Psychological and surgical consultation should also be offered.

Introduction

Thelarche occurs in a predictable time in puberty after or coinciding with the acceleration of growth. The average age of thelarche differs with race, ethnicity and BMI and is considered delayed if breast development has not occurred by age 13. Delayed puberty, including thelarche, occurs in 3% of adolescents. It is most commonly due to a constitutional delay or hypothalamic-pituitary-adrenal axis dysfunction and is treated with low dose estrogen that is discontinued when puberty progresses.¹

Neurofibromatosis type 1 is an inherited autosomal dominant condition occurring 1 in 2500 to 3000 individuals which involves inactivation of the neurofibromin (NF1) gene on chromosome 17. Classically these patients present with peripheral nerve sheath tumors (neurofibromas) and a constellation of other peripheral skin and tissue findings.²

Neuroendocrine conditions including acromegaly have been associated.³ Five to 20 percent

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of patients carry a 1.4Mb deletion of NF1 and its flanking genes (NF1 microdeletion syndrome) which results in an enhanced and more severe phenotype.⁴ Management of neurofibromatosis type 1 is patient specific and focuses on symptomatic treatment of their unique complications.²

Cases of precocious puberty have been highlighted in patients with neurofibromatosis type 1, however an association with delayed puberty, specifically thelarche, has yet to be described.² In patients with unexplained absent thelarche, it is important that reproductive health specialists recognize potential etiologies as well as syndromic associations in order to implement appropriate evaluations and referrals. We describe a case of a 28-year-old woman with neurofibromatosis type 1 and acromegaly who, despite meeting other pubertal milestones and initiating hormonal therapy, failed to develop breasts.

Case

A 28-year-old woman, gravida 0, with neurofibromatosis type 1 and acromegaly presented to the National Institutes of Health in February 2015 to enroll in a natural history protocol. During her evaluation, she was referred to reproductive endocrinology for absent breast development and secondary amenorrhea. She reported menarche at age 12 in the absence of thelarche. Initial menses were reportedly heavy which prompted initiation of combined oral contraceptives containing 30 mcg ethinyl estradiol and 0.3 mg norgestrel. This method successfully regulated her menses for approximately 14 years; however, despite compliant use of the oral contraceptives, she had no stimulation of breast development. She reported normal body hair growth and that all of the women in her family had developed breasts.

She was a well-nourished female standing at 165 cm and weighing 68 kg. She had multiple neurofibromas, an abnormal skull, a classic dysmorphic face, a prominent brow and unilateral sphenoid winging. Physical examination revealed Tanner Stage 1 breasts containing both the nipple and areola. Pubic hair was Tanner Stage V. Laboratory values were within the normal range for a patient on oral contraceptives (FSH 3.6 Units/L, LH 1.4 Units/L, Estradiol <5pg/mL, Progesterone <0.1 ng/mL, TSH 0.56 milli-international units/mL, total testosterone <20ng/dL, prolactin 8.8 mcg/L). Insulin-like growth factor 1 (IGF-1) was elevated at 451 ng/mL and growth hormone was normal at 3.85 ng/mL. MRI and ultrasound of the pelvis revealed small ovaries but a normal uterus.

Secondary amenorrhea was thought to be due to endometrial suppression from long term use of oral contraceptives and she spontaneously resumed menses shortly after discontinuing them. In attempt to induce breast development, she was recommended to start transdermal estrogen supplementation at 6.25mcg daily with a plan to gradually increase the dose over a two-year period, though the patient did not implement this plan and did not start any other regimens of hormonal therapy. Chromosome microarray analysis was also recommended but not performed at that time.

She returned for further evaluation for acromegaly in November of 2016 given her previously elevated IGF-1 and reports of rapidly enlarging hands and feet. No growth charts were available. Twelve-hour serial growth hormone testing was elevated. MRI brain

demonstrated a symmetrical, voluminous pituitary gland measuring $15 \times 9 \times 13$ mm thought to secondary to somatotroph hyperplasia. In response to these clinical and lab findings, she was started on bromocriptine 2.5mg.

She reported no change in breast development upon re-presentation. Laboratory values were repeated and were found to be within normal ranges (FSH 2.7 Units/L, LH 6.5 Units/L, Estradiol 377.4 pg/mL, Progesterone <0.1 ng/mL, TSH 0.89 milli-international units/mL, total testosterone <20ng/dL, prolactin 20.9 mcg/L, ILGF-1 209 ng/mL). She agreed to chromosome and microarray analysis which revealed 46XX karyotype and a 20 gene deletion at 17q11.2 consistent with the NF1 microdeletion syndrome. Genes included were SUZ12P1, ATAD5, TEFM, ADAP2, RNF135, DPRXP4, MIR4733, NF1, OMG, EVI2B, EVI2A, RAB11FIP4, MIR4724, MIRI93A, MIR4725, MIR365B, COPRS, UTP6, SUZ12, and LRRC37B.

She was recommended to continue bromocriptine and initiate continuous combined oral contraceptives due to her desire for complete menstrual suppression. She was counseled that her absent thelarche could not currently be attributed to her other conditions and that her future reproductive potential should not be impacted. Both breast ultrasound and plastic surgery consultation were discussed and patient planned to return for routine endocrine follow up.

Discussion

We describe a case of a woman with neurofibromatosis type 1, acromegaly and the NF1 microdeletion syndrome who failed to develop breasts despite initiation of hormone therapy, the standard treatment for delayed puberty and thelarche. Neurofibromatosis type 1 has been associated with precocious puberty, but to date has not been linked to delayed puberty or thelarche in cases reported in the English language.

The differential to explain isolated absence of thelarche is broad and not frequently reviewed in the literature. The majority of published reports describe cases of congenital breast anomalies affecting mammary tissue (amazia), the nipple-areolar complex (athelia) or both (amastia).^{5, 6} These conditions are rare and are thought to result from failed development of the mammary line due to in utero disruption of the vascular supply to the developing breast.⁷

Congenital breast anomalies are more common in females (male: female 1:5), can be unilateral or bilateral and have been described as having both autosomal recessive or dominant inheritance patterns.^{6, 8, 9} Breast anomalies can be isolated or associated with various syndromes such as Poland sequence, acral-renal ectodermal dysplasia lipoatrophic diabetes (AREDYLD) syndrome, ectodermal dysplasia, and ulnar-mammary syndrome.^{5, 7, 10, 11, 12} First trimester exposure to methimazole, carbimazole and dehydroepiandrosterone have also been linked.¹⁰

To further delineate whether our patient's conditions were responsible for her absent breast development, we performed a PubMed search for cases of isolated absent thelarche using basic search terms such as "absent thelarche," "bilateral absent thelarche," "isolated absent thelarche," "absent breast development," "amastia," in conjunction with "neurofibromatosis"

or “acromegaly.” We also reviewed the Online Mendelian Inheritance in Man (OMIM) genetic assembly for genes included in our patient’s microdeletion and their contributions to breast development.

After an extensive review of the literature, we could find no published cases of a patient with neurofibromatosis type 1 and acromegaly who also had absent thelarche. Upon broadening our search, we found six case reports ranging from 1968 to 2014 describing cases of absent breast development and these are summarized in Table 1. Of the 20 genes comprising our patient’s microdeletion, 13 genes had no demarcated role in mammary development and seven had not yet been described in the genome assembly.¹⁴

We postulate that our patient’s absent breast development is related to one of the congenital anomalies described above. However, given that various other gene deficiencies have been linked to aberrations in mammary development, it is possible that genes in our patient’s microdeletion that have not yet been described could provide an explanation for her absent thelarche.¹⁵ Another rare possibility is that our patient’s breast tissue was deficient for estrogen receptor alpha (ER α) which is critical for proper mammary development, though we discovered that testing to prove this theory was not readily accessible.¹⁶ Ultrasound, mammography, or tissue biopsy could be used to confirm absence of breast tissue, though there are no studies detailing the diagnostic accuracy of these techniques for these patients.⁵ Overall, patients with isolated absent thelarche unresponsive to hormone therapy warrant an extensive genetic analysis, psychological guidance and consideration of surgical reconstruction if the patient so desires.^{5, 10}

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Teaching Points

1. Neurofibromatosis type 1 has been associated with precocious puberty but has not associated with delayed or absent thelarche.
2. Patients with isolated absent thelarche resistant to hormone therapy should be evaluated for congenital anomalies of the breast, estrogen receptor deficiencies or gene defects and offered psychological care and surgical consultation if desiring reconstruction.

Table 1

Other reports of isolated and syndromic cases of absent breast development.

Author	Condition described	Associated features/syndromes	Age at investigation	Presence of menstruation	Family history	Hormonal evaluation	Imaging	Karyotype
Dreifuss et al. ⁵	Congenital amazia	Low set nipples and areola, right foot postaxial polydactyly, bilateral syndactyly of toes, left ptosis, amblyopia, posterior low set ears	13 years	Yes	No	Reportedly normal	Renal Ultrasound: Normal	46XX
Dutta et al. ⁶	Congenital bilateral amastia	Short stature, delayed teeth eruption, high arched palate, absent nipples/areola	9 years	Prepubertal	NA	Reportedly normal	Breast Ultrasound: absent breast tissue, normal pectoralis muscles and subclavian artery Pelvic Ultrasound: Normal	46XX
Patil et al. ⁸	Congenital amastia in mother and newborn daughter	Patient 1 (Mother): High arched palate, depressed nasal bridge, absent nipples/areola Patient 2 (Daughter): depressed nasal bridge	23 years	Yes	Yes	NA	NA	NA
Kowlessar et al. ⁹	Isolated bilateral absence of the breast tissue and nipples in siblings of parents with consanguinity	Patient 1 (Sister): No other abnormal features Patient 2 (Brother): No other abnormal features	3 days	Prepubertal	Yes	NA	Breast Ultrasound: Absent glandular breast tissue, normal subclavian artery doppler bilaterally	46XX
Lin et al. ¹⁰	Complete breast absence in mother and newborn daughter	Patient 1 (Mother): Sensorineural hearing defect, dentinogenesis imperfecta Patient 2 (Daughter): Branchio-oto-renal syndrome, choanal atresia, dentinogenesis imperfecta	1 week	Prepubertal	Yes	NA	NA	46XX
Cogulu et al. ¹³	Absent breast development with history of mandibuloacral dysplasia	Mandibuloacral dysplasia, nipples/areola present	13.7 years	Yes	NA	Reportedly normal	Breast Ultrasound: Absent glandular breast tissue	NA

NA = Not available