Plexiform Neurofibroma of Clitoris

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Abstract

Keywords

- plexiform neurofibroma
- clitoromegaly
- neurofibromatosis
- NF1
- café au lait spots

The most frequent genital presentation of neurofibromatosis in females is clitoromegaly. We report a case of a 5-year-old girl with neurofibromatosis type 1 with clitoral plexiform neurofibromatosis. Clitoroplasty was done, and the histopathology confirmed the diagnosis. Though rare, plexiform neurofibroma of clitoris should always be considered as a differential diagnosis in children with clitoromegaly before embarking on detailed investigations.

Introduction

Neurofibromatosis type 1 (NF1) is an autosomal-dominant disorder with multisystem involvement. The incidence is 1 in 3,500. The *NF1* gene is located on chromosome 17q11.2 and encodes a tumor suppressor protein named neurofibromin. A mutation in the gene leads to uncontrolled cell proliferation with resultant formation of neurofibromas. Plexiform neurofibroma (PN) which is pathognomonic of NF1 can involve any organ in the body. Genital involvement is rare, and clitoral involvement is the most common presentation in females. We report a case of a 5-year-old girl with NF1 who presented with clitoromegaly.

Case Report

A 5-year-old girl, who was the second child of nonconsanguineous parents, was referred for evaluation of ambiguous genitalia. Clitoromegaly was noticed from 1.5 years of age and was gradually increasing in size. There was no history of

exposure to androgens or progesterone or gestational luteoma. She had normal intelligence. Examination of the genitalia revealed a phallus-like structure measuring 3.5 cm with no palpable gonads (►Fig. 1A). She had multiple (> 15) café-au-lait spots all over the body, the largest being 6.5 × 8 cm, and a small neurofibroma over the right buttock. Her bone age corresponded to her chronological age. There were no signs of virilization. A detailed pedigree analysis revealed that her mother, maternal twin sister and her offspring had clinical features consistent with NF1 (►Fig. 2).

Laboratory investigations revealed undetectable levels of testosterone, < 0.45 nmol/L (below the lower limit of detection), normal levels of dehydroepiandrosterone 5.85 µg/dL (normal 2.3–15 µg/dL) and 17-hydroxyprogesterone 10 ng/dL (normal 3–90 ng/dL) for age. The clitoral reduction was done, and the neurofibroma was found to be arising from the clitoral body and corpus cavernosum whereas the clitoral glans was free. The histopathology revealed tortuous nerve bundles with many Wagner–Meissner bodies (►Fig. 1B), thus confirming the diagnosis of PN of the clitoris. Stroma

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Fig. 1 (A) Clitoromegaly with pseudopenis appearance. Note the café-au-lait spots over the medial aspects of both thighs. (B) Histopathology showing tortuous nerve bundles (thin arrow) and Wagner-Meissner bodies (thick arrow), which are characteristic features of plexiform neurofibroma (hematoxylin and eosin stain $\times 400$).

showed plasma cells, lymphocytes, and mast cells with no atypia or mitosis, thereby ruling out the malignant transformation.

Discussion

Around 30 to 50% of patients with NF1 have plexiform neurofibromas,¹ which usually arise along the course of a peripheral nerve. Plexiform type of neurofibroma is more common than the nodular type when the lesion involves the urogenital area. Involvement of the external genitalia is rare, but when present, females outnumber males.² The most frequent presenting sign is clitoromegaly with pseudopenis in females and enlarged penis in males. Extensive innervation of the clitoris makes it a common site for hamartomatous overgrowth.

Haddad and Jones first reported clitoral neurofibroma.³ The incidence of clitoral involvement in NF1 is unknown, but the incidence of genital involvement in both sexes has been

estimated as 1.8%.⁴ In a series of 620 patients with NF1, only 4 patients had neurofibroma of the genitalia, which indicates an extremely low prevalence of 0.65%.⁵ Apart from the clitoris, the other sites of involvement include the labia majora, mons pubis, cervix, uterus, and ovaries. It can also extend into the bladder, ureters, or retroperitoneum.^{5,6} The glans clitoris is usually affected in NF1, but in our case, the clitoral body was involved; only two such cases have been reported so far.⁷

The asymptomatic nature of clitoromegaly leads to delay in seeking medical attention, which might be a cause for underreporting of this entity. PN of external genitalia has a propensity for the contiguous involvement of the bladder and ureter, especially when there is a delay in seeking medical attention.⁸ Hence, magnetic resonance imaging (MRI) is important to evaluate the extension of the lesion. In our case, MRI of the pelvis was not performed, but ultrasound of the abdomen did not show any extension of the lesion to the bladder or other pelvic structures.

Malignant transformation of clitoral neurofibroma is extremely rare, but a single case has been reported, where malignant schwannomatous change had occurred in association with clitoral involvement in a 1-year-old girl.⁹ Hence, it is prudent to do a histopathological evaluation, even if the patient has features consistent with NF1.

Clitoroplasty with preservation of the neurovascular bundle and glandular tissue is the treatment of choice for clitoral neurofibroma.^{4,10} The patient should be kept under follow-up for recurrence, which is usual if the excision of the primary lesion was incomplete.⁶

Endocrinological evaluations help to differentiate clitoromegaly due to NF1 from the virilizing type of congenital adrenal hyperplasia, virilizing ovarian tumors, the effect of exogenous maternal hormones and maternal drug exposure. Examining first-degree relatives for evidence of NF1 can obviate extensive evaluation. The firm consistency of the enlarged clitoris due to underlying PN provides a good clue

Fig. 2 Pedigree showing affected members: II 4, II 5, III 2, and III 4 (proband).

for differentiating it from other causes of clitoromegaly. Clitoral PN should be a differential diagnosis in all cases of clitoromegaly, even in the absence of a positive family history, once other causes of virilization have been ruled out.

Authors' Contributions

D.Y. prepared the article and did a detailed literature search. B.S. was the surgeon and also contributed to the surgical details in the article. A.J. contributed to the histopathological aspects in the article. M.A. has critically evaluated the article and has contributed suggestions. N. B. had evaluated the case in detail and had helped in article preparation. H.M. has done a literature review and has contributed suggestions. S.N. had conceived the idea of drafting this article and had done the final drafting and will act as the guarantor of the article.

Conflict of Interest

None.

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