

Magnetic resonance neurographic confirmation of extensive Plexiform neurofibroma in neurofibromatosis-1 presenting as ambiguous genitalia

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Abstract

Genitourinary involvement of neurofibromatosis is uncommon and genital neurofibromatosis is even rarer. Involvement of clitoris by neurofibroma can lead to clitoromegaly masquerading as a male penis. We report such a case of ambiguous genitalia in a 7-year-old female child presenting with clitoromegaly since birth, in which magnetic resonance imaging (MRI) revealed the presence of extensive neurofibromatosis in the clitoris and lumbosacral regions. We emphasize the central role of MRI in evaluation of hormonal and non-hormonal causes of ambiguous genitalia. We further discuss the merits of including MR neurography in the imaging protocol for comprehensive delineation of neurofibromatosis.

Key words: Clitoromegaly; genital neurofibromatosis; MR neurography

Introduction

Birth of a child with ambiguous genitalia often imparts great deal of apprehension and confusion to the involved families. Diagnostic workup and timely designation of the gender to these patients is indispensable for healthy psychological and physical growth. Clitoromegaly refers to an abnormal enlargement of a female clitoris, thus masquerading as a male penis. Most of the cases of clitoromegaly in pediatric age group are attributed to hormonal etiologies with minority of cases affected by nonhormonal causes such as neoplastic infiltration.^[1] Although complete diagnostic workup of these patients consists of extensive hormonal and chromosomal assays,

in practice, pelvic imaging constitutes a vital preliminary step in evaluation. Because of unparalleled tissue characterization and multiplaner capabilities, pelvic magnetic resonance imaging (MRI) not only adequately depicts the urogenital anatomy in the hormonal causes of female virilization but also aids in surgical planning.^[2] Moreover, amongst the nonhormonal etiologies, MRI can also comprehensively delineate mass lesions infiltrating the clitoris.

In this report, we present such a case of ambiguous genitalia in a female baby with congenital clitoromegaly, in which pelvic MRI and MR neurography revealed the presence of

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extensive neurofibromatosis in the clitoris and lumbosacral regions.

Case Report

A 7-year-old child presented to the outpatient department of Endocrinology clinic of our hospital for evaluation of ambiguous genitalia and intersex state. On physical examination [Figure 1], there was presence of multiple light to dark brown patches of pigmentations in the lower abdomen, perineal region, bilateral groins, and upper thighs. There was a lobular swelling in the right thigh. Ophthalmological examination revealed no significant abnormality. There were no first degree relatives with similar complaints. The examination of genital region revealed a small penis that looked like an enlarged clitoris, with small scrotum that was separated and looked like labia. No testes were present within the scrotum. The urethral opening was located posterior to the penis. Based on the clinical examination, the child was presumed to be genetic male and referred for karyotyping and ultrasound of pelvis to look for undescended testes. However, the patients karyotype came out to be 46XX and pelvic sonography revealed normal appearing uterus and bilateral ovaries. Moreover, ultrasonography showed diffusely thickened bladder wall with sacculations and trabeculations. Endocrine evaluation was done that ruled out precocious puberty, congenital adrenal hyperplasia, and other hormonal causes of clitoromegaly. Lumbosacral plain radiographs were obtained which showed widened neural foraminae at the sacral vertebral level [Figure 2]. No other osseous lesions were present. MRI was performed on a 1.5 T superconducting system (Magnetom Avanto, Seimens Medical System, Erlangen, Germany). Routine pelvic MR scan was performed using body array coil with

respiratory gating. The scan was performed in supine position after cushioning the legs with arms folded on the chest. Patient was given ear protectors. The sequences used were FSE T2 sagittal, axial with fat saturation, and coronal with fat suppression, and SE T1 coronal and axial with post contrast images. Postcontrast volume extrapolated breath-hold examination (VIBE) axial and coronal images were also obtained with fat suppression. Pelvic MRI (sagittal T2 weighted images (WI) and coronal T1W sequences) confirmed the presence of a uterus measuring approximately 5 × 1.5 × 1.5 cm (appropriate for age) with normally visualized vagina and bilateral ovaries. T2W images showed homogenous lobulated mass lesions in bilateral sacral neural foraminae extending along bilateral lumbosacral plexus. Distal extent of these masses, however, could not be delineated on these images. MR neurography [Figures 3 and 4] of lumbosacral and thigh regions was performed using three-dimensional (3D) Short tau inversion recovery sampling perfection with application-optimized contrasts using varying flip-angle evolutions (STIR-SPACE), which revealed the presence of multiple, lobulated, homogenous mass lesions long the nerve roots of bilateral lumbosacral plexus, bilateral sacral neural foraminae, extending into right thigh along the femoral nerve and bilateral broad ligament. A similar signal intensity and enhancement pattern was also noted



Figure 1: Clinical picture of the patient. Multiple brown patches of pigmentations are seen in the lower abdomen, perineal region, bilateral groins, and upper thighs. There was a lobular swelling in the right thigh along with ambiguous genitalia



Figure 2: Plain lateral radiograph of lumbosacral region shows widened sacral neural foramina (arrow)



Figure 3: MR neurography: enlarged lobulated, serpentine, homogenous mass lesions are seen along the nerve roots of bilateral lumbosacral plexus, bilateral sacral neural foraminae, extending into bilateral thighs along femoral nerves which represent plexiform neurofibromas (arrows). Note is also made of similar subcutaneous lesion in right medial thigh (arrow)

within the hypertrophied clitoris and bilateral mass lesion measuring approximately $5 \times 2 \times 4$ cm was seen involving clitoris and bilateral labial tissue. Urinary bladder was grossly distended with diffuse, irregular wall thickening suggesting neurogenic bladder. A provisional diagnosis of neurofibromatosis-1 was given based on the MRI picture of plexiform neurofibroma and presence of extensive café au lait spots. The patient was referred to pediatric surgery department where excision of the clitoris mass was done with clitoroplasty. Histopathological examination confirmed corpus cavernous tissue infiltrated by a plexiform neurofibroma.

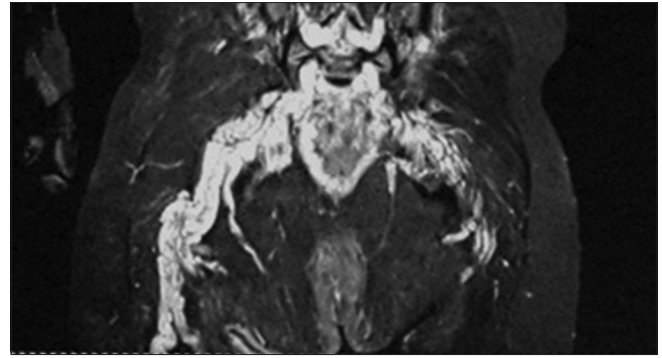


Figure 4: MR neurography: hyperintense mass lesion is seen involving the clitoris (arrow). Serpentine lobulated hyperintense masses along the bilateral lumbosacral plexus can also be seen clearly

Discussion

Imaging forms an important step in the assessment of internal urogenital anatomy in a child with ambiguous external genitalia. Ultrasound (US) still forms the first step in imaging of these patients for reasons beyond its widespread availability, primarily because complete screening of inguinal, perineal, renal, and adrenal regions can be performed quickly in the same examination. Notwithstanding the initial evaluation, MRI has a dominant status as the problem solving tool, contributing to the accurate morphologic evaluation of müllerian duct structures, the gonads, and the development of the phallus.^[2]

A simple and elegant imaging algorithm has been suggested by Chavhan *et al.*^[3] for evaluation of children with ambiguous genitalia. Palpable gonads confirmed as testes on US, along with absence of uterus and ovaries should be diagnosed as male pseudohermaphrodite. However, presence of scrotal or abdominal testis along with demonstration of uterus on imaging, points toward the diagnosis of persistent müllerian duct syndrome, mixed gonadal dysgenesis or true hermaphroditism, depending on the absence of ovary, presence of extra streak gonad or an extra ovotestes, respectively. Absence of palpable gonad or intraabdominal testes, along with US demonstration of uterus and ovaries should be assigned as female pseudohermaphrodite. In cases where US fails to demonstrate ovary in setting of well visualized uterus, MRI should be performed to search for ovarian tissue before labelling the case as pure gonadal dysgenesis in which streak gonads are present instead.^[3]

Clitoromegaly associated with female pseudohermaphroditism (46, XX) is defined as clitoral index (length \times width) more than 15 mm^2 in a neonate.^[4] Poorly delineated supporting structures on MRI such as bulbospongiosus, transverse perineal muscles provide a clue to differentiate hypertrophied clitoris from a normal penis.^[3,5] Congenital enlargement of clitoris is most commonly caused by congenital adrenal hyperplasia or enzyme defect in pathways of steroid

biosynthesis. Less frequently, various nonhormonal conditions such as neurofibromatosis, epidermoidcysts, hemangiomas, nevuslipomatous cutaneous superficialis are reported causes implicated in clitoromegaly.^[6] Isolated case reports of other lesions such as abscess, transitional cell carcinoma, melanoma, and lymphoma are also described in the literature.^[7,8] As was in our case, imaging is vital and often first to point out such diagnoses.

Plexiform neurofibromas, in the setting of neurofibromatosis type I, are the most commonly reported neoplasm of clitoris, thus resulting into female pseudohermaphroditism.^[9-13] Although conventional MR sequences have been traditionally considered as the gold standard for diagnosis of neurofibromatosis, recent advent of MR neurography has imparted improved confidence in diagnosis and in aiding surgical planning through its multiplaner capabilities, precise and complete lesion localization, elegant tissue characterization and absence of partial volume averaging compared to conventional sequences. This nerve selective imaging technique employs diffusion weighting in conjunction with anatomic sequences. Unidirectional motion probing gradient with higher diffusion moment (b value >800 s/mm²) is applied in anteroposterior direction in the axial plane as diffusion is more restricted across the nerve.^[14] Postprocessing is required to suppress signals from vessels. The authors have used 3D STIR SPACE (sampling perfection with application optimized contrasts using varying flip angle evolutions) in the index case, which is used in the imaging of nerve plexuses. Other sequences available for neuronal MR imaging are 3D SPAIR SPACE, 3D T2 SPACE, and 3D CISS which are deployed in the evaluation of extremities, spinal cord (MR myelography), and cranial nerves, respectively.^[14] As in the present case, 3D images generated by MR neurography can elegantly demonstrate exact extent of the lesion with recognition of even subtle alterations in contour and thickness of the involved nerves. Besides differentiation from other mimicking vascular and lymphatic lesions, MR neurography can also display otherwise inconspicuous internal fascicular structure of the neural lesion, disruption of which indicates towards malignant peripheral nerve sheath tumors in NF1.^[15,16] Recent literature also describes the use of diffusion tensor imaging as useful adjunct in MR neurography to interrogate microarchitecture of the nerves involved.^[13,14]

Involvement of genitourinary system is rare in neurofibromatosis syndromes with reported prevalence of 0.65%,^[11] commonly involving urinary bladder and ureters. Genital involvement in neurofibromatosis is even more infrequently encountered, although reported more commonly in females with clitoromegaly being the most common.^[10,11] However, Sutphen *et al.*^[12] in his study over 236 families of neurofibromatosis-1 concluded that clitoris involvement in neurofibromatosis-1 might be

more common than reported. Less than 40 cases of genital neurofibromatosis have been reported till date, with most common involvement of clitoris, labia majora, prepuce, and unilateral labia in that order. Genital involvement in males is commonly related to the involvement of penis and is mostly associated with concomitant genitourinary involvement.^[11] Concomitant involvement of external genital system and lumbosacral region is previously only once reported with the involvement of the left half of penis and left lumbosacral plexus in a male patient. To the best of our knowledge, the present case is the first to have concomitantly involved external genitalia and lumbosacral plexus in a female patient.

An important aspect of the index case was presence of neurogenic bladder, possibly owing to tumor infiltration of lumbosacral plexus. In the setting of neurofibromatosis, clinical and radiological features of bladder outlet obstruction have been reported in a few isolated case reports in which urinary retention were either attributed to tumor infiltration of bladder neck and prostatic urethra^[17] or due to involvement of nerves supplying the bladder.^[18]

The differential consideration of neurofibromatosis as a possible cause of clitoromegaly may help avoid exhaustive and unnecessary investigations.^[13] Considering that neurofibromatosis is one of the most common causes when clitoromegaly is caused by tumor infiltration, imaging should always be performed to look for presence of any abnormal mass lesion in the common locations, especially when accompanied by cutaneous lesions. Our case report adds to the scant literature about the association of genital neurofibromatosis causing clitoromegaly, and highlights the crucial role of MRI in assessment of both common and unpredictable etiologies leading to ambiguous genitalia. The present case also describes the utility of MR neurography as a problem solving tool and a useful adjunct to the conventional MRI in augmenting the diagnostic confidence in cases of neurofibromatosis.

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Conflicts of interest

There are no conflicts of interest.

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