

# Bladder Plexiform Neurofibroma in Neurofibromatosis Carrier: a Case Report

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*Neurofibroma Plexiforme Vesical em Portador de Neurofibromatose: Relato de caso*

Neurofibroma Plexiforme Vesical en Portador de Neurofibromatosis: Relato de Caso

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## Abstract

**Introduction:** Type 1 neurofibromatosis is an inherited autosomal dominant disease with complete penetrance and is related to mutations in the NF1 gene (17q11.2). It presents extremely variable expression and predisposition to the occurrence of tumors. Complications such as visceral neurofibromas occurs in only 1% of NF1 cases. Vesical neurofibromas are extremely rare. **Case report:** Here in, we expose a case of a 4 years old boy, who presented signs and symptoms of urinary and intestinal dysfunction associated with lumbosacral spine deviation. His physical exam had neurofibromatosis type 1 features and the complementary exams revealed a vesical neurofibroma. Subsequently, a neurofibromatosis type 1 diagnosis was performed. **Conclusion:** Diagnose tumor predisposing syndromes and associated complications is essential for these patients.

**Key words:** Neurofibromatosis 1; Neurofibroma, Plexiform; Urologic Neoplasms.

## Resumo

**Introdução:** A neurofibromatose do tipo 1 (NF1) é uma doença hereditária de caráter autossômico dominante, com penetrância completa e relacionada a mutações no gene NF1 (17q11.2). Apresenta expressão extremamente variável e predisposição à ocorrência de tumores. Complicações como neurofibromas viscerais estão presentes em apenas 1% dos casos de NF1. Neurofibromas vesicais são extremamente raros. **Relato do caso:** O presente caso faz referência a um paciente do sexo masculino com 4 anos de idade que apresentava sinais e sintomas de disfunção urinária e intestinal associados a desvio da coluna lombossacra. Ao exame, foram identificadas características típicas de NF1 e os exames complementares permitiram o diagnóstico de um neurofibroma vesical. Posteriormente, foi concluído o diagnóstico de NF1. **Conclusão:** O diagnóstico de síndromes predisponentes ao câncer e o rastreamento de tumores associados a essas condições são essenciais aos portadores dessas doenças.

**Palavras-chave:** Neurofibromatose 1; Neurofibroma Plexiforme; Neoplasias Urológicas.

## Resumen

**Introducción:** La neurofibromatosis tipo 1 es una enfermedad hereditaria de carácter autosómico dominante, con penetración completa y relacionada con mutaciones en el gen NF1 (17q11.2). Se presenta una expresión extremadamente variable y predisposición a la ocurrencia de tumores. Las complicaciones como los neurofibromas viscerales están presentes en sólo el 1% de los casos de NF1. Los neurofibromas vesicales son extremadamente raros. **Relato del caso:** Exponemos el caso de un niño de 4 años que presentaba signos y síntomas de disfunción urinaria e intestinal asociados a la desviación de la columna lumbosacra. En el examen se identificaron características típicas de neurofibromatosis y los exámenes complementarios permitieron el diagnóstico de un neurofibroma vesical. Se ha concluido el diagnóstico de neurofibromatosis del tipo 1. **Conclusión:** Diagnosticar los síndromes predisponentes del tumor y las complicaciones asociadas son esenciales para estos pacientes.

**Palabras clave:** Neurofibromatosis 1; Neurofibroma Plexiforme; Neoplasias Urológicas.

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## INTRODUCTION

Type 1 neurofibromatosis (NF1) is an inherited autosomal dominant disease caused by mutation of the gene NF1. Half of the cases occurs because of new mutations<sup>2</sup>.

The clinical diagnostic criteria of the disease were established in the Consensus of the *National Institute of Health* (NIH)<sup>3</sup>. Among them, is the presence of at least one plexiform neurofibromatosis (NFP). External NFP can be noticed in the physical exam<sup>4</sup>; however, the diagnosis of internal NFP depends on clinical suspicion and image methods<sup>5,6</sup>.

The present report describes the presence of vesical NFP in a child with NF1.

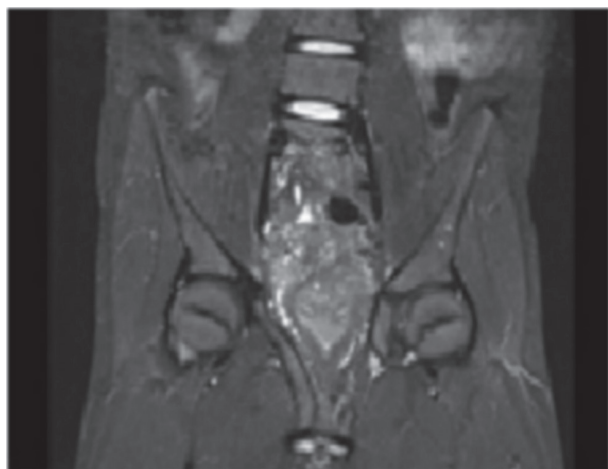
## CASE REPORT

Male patient, 4 years old, attended on August 5, 2011 at “Instituto Nacional de Câncer José Alencar Gomes de Alencar (INCA)” because of urinary urgency and anal sphincter dysfunction.

The pelvic ultrasound showed infiltrative aspect tissue in the posterior bladder wall. There was a voluminous expansive formation at the pelvis, between the rectum and the bladder shown in the computerized tomography. The magnetic resonance showed an expansive and infiltrative formation in the posterolateral and upper anterior wall, seminal vesicles, prostate and rectal mass (Figure 1).

It was carried out an exploratory laparotomy and biopsy for diagnosis clarification. The anatomopathological examination revealed NFP.

The patient was the third child of non-consanguineous parents, without family background of similar cases. In the physical exam, it was found claudication, lumbosacral



**Figure 1.** Scar of exploratory laparotomy approach, evidencing pelvic voluminous mass with nearly 12 cm

NFP, *café-au-lait* spots of variable sizes (bigger than 0.5 cm) in the whole body, hypertrichosis in the sacral region (Figure 2), mass in scrotal pouch at right and palpable bladder (Figure 2). Because of the clinical status, it were diagnosed NF1 and screening of other signs of the disease. The ophthalmic and radiographic evaluations were normal.



**Figure 2.** Computerized tomography in sagittal cut with expansive injury in lower abdomen with peritoneal implants

The patient is in follow up with INCA genetic, surgical and pediatric team.

The present study is part of the trial “Clinical and molecular characterization of the hereditary cancer: National Network of Family Cancer “. The Institutional Review Board of INCA approved the study, number CEP/INCA: 114/07. The responsible for the child granted authorization for publication through the signature of an Informed Consent Form.

## DISCUSSION

A patient with NF1 was reported. The diagnosis of NF1 is based in clinical findings. The criteria were established in 1980 a NIH Consensus. Seven diagnostic characteristics were agreed about the disease: six or more *café-au-lait* skin macules greater than 0.5 cm in childhood or 1.5 cm postpubertal; two or more nodes of Lisch; bone alterations (sphenoid wing dysplasia or tibial pseudarthrosis); two or more neurofibromatosis or one NFP; freckling in axillary or inguinal, optic nerve gliomas and first-degree relatives by the criteria for NF1<sup>3</sup>. All the patients manifested variable characteristics<sup>7</sup>; because of this, it were necessary two criteria for diagnosis. For the case in question, diffuse >0.5 cm length *café-au-lait* macules and extensive NFP are diagnosis of the disease.

NF1 is caused by pathogenic mutations of gene NF1. NF1 is a large gene (350 kb, 57 exons NM\_000267.3)

present in the long arm of the chromosome 17 (17q11.2), which codifies the protein neurofibromin, whose function is to inhibit the expression of the gene Ras. In the presence of mutations in the gene NF1, the neurofibromin loses its functions and gene Ras starts to stimulate the multiplication and disordered cell growth<sup>8</sup>. It is worth mentioning that the gene has complete penetrance, therefore, all the patients with mutations of the gene NF1 have manifestations of NF1. The molecular assessment is considered in the suspected cases that fail to meet the NIH-defined criteria.

The loss of function of the gene NF1 increases the susceptibility to the development of benign and malignant tumors of the peripheral and central nervous system<sup>9</sup>. It is estimated that half of the cases of NF1 has plexiform neurofibromatosis<sup>6,10,11</sup>. The NFP are benign tumors that develop in the neural sheaths of the fascicular and branches nerve. Overall, they affect trigeminal or upper cervical nerves and are characterized histologically as elongated fibromatosis<sup>12</sup>. In the visceral cases, clinical suspicion is of essence. The boy in question initiated his condition with urinary urgency and anal sphincter dysfunction that are common symptoms of vesical NFP presentation<sup>13,14</sup>. Curiously, bladder NFP are more frequent in males (2:1)<sup>15</sup>.

Because of NFP suspicion, the combination of imaging methods (ultrasound, computerized tomography and magnetic resonance) is able to reveal<sup>16-18</sup>. Magnetic resonance is the method of choice for the diagnosis of plexiform neurofibromatosis and to distinguish nature and tumoral extension<sup>19,20</sup>. The positron emission tomography (PET-CT) helps to differentiate benign or malignant peripheral sheath nerve tumors<sup>21,22</sup>. However, clinical symptoms of augmentation of volume, pain or persistence of doubt about the diagnosis indicates biopsy for a definitive differentiation through histologic examination of the tumor<sup>23</sup>.

In literature, it has been reported surgical and expectant conducts for cases of NFP<sup>24-26</sup>. Pediatric patients with internal and extensive NFP, as in this case, have greater risk of postoperative complications and elevate rate of new tumoral growth<sup>11,27,28</sup>. Therefore, the clinical observation and image testing were carried out with this patient.

The surveillance of the patients with NFP is a relevant topic because of the potential malignancy. Case reports indicate the onset of malignant tumors of the peripheral nerve sheath in patients with bladder NFP<sup>29-31</sup>. These cancers are extremely aggressive and appear in approximately 10% of the affected<sup>32</sup> and within an early age range in comparison to the sporadic in the general population<sup>33</sup>. The case did not present signs of malignancy so far.

Various clinical trials for NFP drug treatment are still ongoing (Phase 2). It is possible to mention those which are based in AKT/mTOR inhibitors drugs (sirolimus) and Raf/MEK/ERK (selumetinib) that are activated as effect of hyper activation of the gene RAS because of the deficiency of the gene NF1. The expected effect is the reduction of the cell proliferation and volume of plexiform neurofibromatosis<sup>34-36</sup>.

## CONCLUSION

NF1 is a disease related to child and adult morbimortality and TENDS to present higher mortality rates among the patients with NFP associated<sup>37</sup>. Furthermore, the patients with NF1 and NFP present high frequency of other NF1-associated tumors NF1<sup>38</sup>. So, whereas the high rate of complications, it is important to point out the necessity of a precise and early diagnosis. To reach this goal, it is mandatory that general practitioners and pediatricians are trained periodically for early identification of the signs and symptoms of the disease. In addition, the patients with this genetic condition should be continuously and carefully followed up to diagnose and treat the conditions that may evolve to irreversible damages like, for instance, NFP and malignant tumors.

## CONTRIBUTIONS

All the authors have contributed substantially for the study planning, data gathering, analysis and interpretation, wording of the manuscript and final approval of the version published.

## DECLARATION OF CONFLICT OF INTERESTS

There are no conflict of interests to declare.

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