

Mini Review: Potential Role of Hormones in The Tumors of Neurofibromatosis Type-1

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Abstract

Neurofibromatosis type 1 is an autosomal dominant neurocutaneous disorder caused by mutations in the NF1 gene, and presents a very broad spectrum of clinical manifestations and severity, including dermal and plexiform neurofibromas. In this mini review we briefly address the findings present in the literature related to hormone receptors within these tumor types.

Keywords: Neurofibromatosis type 1; Neurocutaneous disorder; Neurofibromas; Hormonal contraceptives

Introduction

Neurofibromatosis type 1 is an autosomal dominant neurocutaneous disorder caused by mutations in the NF1 gene which codes for neurofibromin, a Ras regulating protein. NF1 is a very prevalent condition, arising in 1:2500 births as a result of either inherited (50% of cases) or *de novo* (50% of cases) mutations, and presents a very broad spectrum of clinical manifestations and severity. These include, but are not limited to, inguinal and axillary freckling, café-au-lait spots, congenital bone defects, scoliosis, optic gliomas, learning disabilities, dermal and plexiform neurofibromas [1].

Neurofibromas and Plexiform Neurofibromas in NF1

Neurofibromas are benign tumors arising from the peripheral nerve sheath. They may be focal tumors (discrete neurofibroma) or extend along the length of a nerve (plexiform neurofibroma) [2]. Discrete neurofibromas are more commonly located in the skin. They may occur just beneath the skin (subcutaneous neurofibromas) or on the surface (cutaneous neurofibroma). While a hallmark of NF1, focal solitary neurofibromas may also be present in unaffected individuals. Neurofibromas are composed of multiple cell types: Schwann cells, fibroblasts, mast cells, perineurial cells, as well as vascular components. Although these tumors are benign, and generally do not exceed 3cm in diameter, dermal neurofibromas may be present from a few to thousands covering the body surface, associated with disfigurement and discomfort [3]. Dermal neurofibromas are rarely present at birth, and their size and number increase over time, with nearly all adults NF1 patients presenting neurofibromas. They are cited as one of the most significant burdens of living with NF1 due to the cosmetic, physical, and functional alterations they may cause [3].

Plexiform neurofibromas on the other hand arise from peripheral nerve sheath either close to the skin or internally and can present uncontrolled growth associated with important clinical complications, invading surrounding structures, causing disfigurement and impacting the organs and tissues encroached upon. Plexiform neurofibromas also carry a 10% lifetime risk of malignant transformation, unlike dermal neurofibromas usually remain benign throughout a patient's lifetime [4].

Hormonal receptors in Neurofibromas and Plexiform Neurofibromas: Literature findings

Anecdotal evidence and case reports have indicated an increase

in neurofibroma number and size during periods of physiological hormonal changes: puberty, menopause, and pregnancy, with some evidence of postnatal reduction in neurofibroma size [2,5,6]. In light of these observations some investigators have investigated the presence of steroid and growth hormone receptors in the neurofibromas of NF1 patients. Growth hormone receptors (GHRs) were detected in the dermal neurofibromas of NF1 patients at a higher rate as compared to that observed within solitary neurofibromas of non-NF1 patients [7]. GHRs are also expressed in plexiform neurofibromas.

It is known that the majority of neurofibromas express progesterone and androgen receptors and *in vitro* and *in vivo* studies have shown that neurofibromas grow in the presence of these hormones. A minority of neurofibromas express the classical estrogen receptor [8,9]. It is interesting to note that a recent study by Dagalakis et al. found no correlation between plexiform neurofibroma growth and puberty onset among 41 NF1 patients, suggesting that the hormonal fluctuations occurring during puberty do not stimulate plexiform neurofibroma proliferation [10]. A search for a similar study involving plexiform neurofibroma growth during pregnancy yielded no results on the databases searched (Pubmed, SciElo).

There is sufficient anecdotal and clinical evidence to warrant further investigation into the role of circulating hormones in dermal neurofibromas. The results of these future studies may impact our understanding of the environmental and hormonal factors contributing to neurofibroma emergence and growth. This understanding is also extremely important to healthcare providers who follow-up NF1 patients, often over many years, beginning from initial diagnosis during childhood. A frequent question raised by NF1 patients regards the use of hormonal contraceptives and the potential impact of these drugs on neurofibroma growth and development [2,11]. Additionally, short

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stature is a common feature of NF1 and many families express interest in pursuing treatment with recombinant growth hormone [2,7]. A 2005 survey of 59 NF1 patients reported no apparent correlation between hormonal contraceptive use and neurofibroma emergence and growth, although this study was based solely on a posteriori patient observations and questionnaires [11].

Conclusion

Previous studies have shown presence of hormone receptors – most notably progesterone receptor and growth hormone receptor – within the neurofibromas and plexiform neurofibromas of NF1 patients. Further studies are warranted to investigate the role of these hormones in the natural history of neurofibromatosis type 1.

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