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Review Article

NF1 Clinical Elements and The NF1 Neurofibroma Burden

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Abstract

In order to understand the elements of the NF1 syndrome, we must recognize the three distinct types of these elements, namely, features, consequences and complications. These distinctions become even more cogent and compelling when we consider the NF1 neurofibroma burden and potential treatment strategies to minimize that burden.

Introduction

As we explore NF1 pathogenetic mechanisms as one approach to deriving various NF1 treatment options, we must first consider each of the disorder's elements we are trying to treat, respecting that there are three basic elements of all genetic disorders, namely features, consequences and complications, as characterized by Riccardi in 2010 [1]. For example, the NF1 feature of vertebral dysplasia often has the consequence of dystrophic scoliosis, which in turn might result in the complication of spinal cord compression. In addition, there may be clinically relevant elements present that are purely coincidental, either as normal variants or coincidental additional conditions, genetic and otherwise [2].

I will not be discussing the genomic aspects of NF1 neurofibroma development other than to consider the notion of the praxitype [3] and to acknowledge that *NF1* gene somatic mutations occur – deriving diploinsufficiency from haploinsufficiency – sometime in the progression of at least a portion of these lesions. It is important that only *some* neurofibromas manifest a "second hit"[4-6]. Contrary to the dogma that has developed in these regards – i.e., the insistence that diploinsufficiency *initiates* the NF1 neurofibroma – I hold that the NF1 neurofibroma ordinarily initiates as a "wound" (mechanical, metabolic, hypoxic) [7,8], while still *NF1* haploinsufficient and that *NF1* diploinsufficiency develops sometime later[4]. This latter approach allows for preemption of *NF1* neurofibroma progression that involves conversion of *NF1* haploinsufficiency to *NF1* diploinsufficiency. In turn, this preemption is a key goal of NF1 neurofibroma treatment aimed at minimizing the fact and nature of the NF1 neurofibroma burden.

Treatment Goals

First, we must consider the *goal* of each treatment, differentiating five potential goals: 1) preemption, 2) arrest, 3) reversal, 4) reduction and 5) palliation. In addition, certain particular findings (of whichever element category) might not be selected for treatment. For example, the feature, café-au-lait spots (CLS), is not ordinarily a treatment target or goal. And, finally, some clinical findings may *not* yet be recognized as warranting treatment consideration, for example, changes in the ocular choroid requiring complex investigation [9-11].

Preemption is a particular type of prevention wherein the process of initiation or early progress is avoided or abrogated. For example, preemption may contribute to fewer numbers of and less advanced progression of NF1 cutaneous neurofibromas (CN) following treatment with ketotifen [12].

Arrest is another type of prevention, one wherein progression beyond the earliest stages of the lesion is circumvented. Arrest likely contributes the fact that very early and prolonged treatment with ketotifen (e.g., 30 years, initiated in infancy) allows both for only for very immature NF1 CN (3-4

mm in diameter and totally flat, and none sessile or pedunculated) and for retarded diffuse plexiform neurofibroma (DPN) growth [12].

Reversal interferes with the lesion once it has achieved its mature, perhaps most flagrant, state and terminates further progression (e.g., neurofibroma growth, malignant transformation) and affords stability or even a decrease in size. Such results have been partially achieved with sunitinib[13], sirolimus[14] or imatinib[15] treatment of large and aggressive NF1 DPN.

Reduction in size of large NF1 neurofibromas, especially DPNs, except as just noted, is mainly effected by surgery [16-19]. As well, NF1 neurofibrosarcomas and related malignancies may be reduced in size by surgery and/or chemotherapy [20, 21].

Palliation as a treatment modality simply involves making the patient more comfortable as he or she succumbs to the disorder and its complications (sensu strictu). An example would be simply alleviating severe pain without altering the source of the pain. Ordinarily, this approach is reserved for the terminal stages of the disorder or the complication.

Non-surgical approaches, particularly *pharmaceutical* ones, specific for NF1 neurofibromas are best directed at the features and consequences. But, accounting for these gene-proximate features requires knowing how the mutant gene is "*put into practice.*" Knowing the details of the mutation may not be enough. For example, I recently engaged a family whose NF1 son had an early-onset intracranial glioma and then a fatal glioblastoma multiforme at age 30 years, while his mother – with the same mutation – is virtually asymptomatic in her 60s. It's not the gene or the mutation simply in terms of DNA base sequences, but how the coded material is put into practice, how we consider its *praxitypes*, that is, the biochemical networks through which the NF1 gene, including any mutant form, is "put into practice"[3,22].

Neurofibroma Burden – Qualitative & Quantitative

In reading about NF1, especially when the primary concern is management, it is fairly common to come across the phrase, "neurofibroma burden." And it's a very important phrase, since it accounts for one of the key determinants of NF1's morbidly and mortality. Yet, despite its importance, there has not been any consensus definition or characterization of the phrase to give it more utility from one publication to another. For example, I recently published on the efficacy of ketotifen for preempting and arresting a potentially high NF1 neurofibroma burden [12]. Is this the "same" high NF1 neurofibroma burden considered in similar discourses on this aspect of NF1 [23-26]? First, there is the amount of the NF1 *feature* [1], the neurofibroma tissue, both in terms of the number of neurofibromas of all types and their cumulative weight, surface area or volume[26]. Second, there are neurofibroma consequences [1], reflecting maturation of the NF1 neurofibromas, including potential compromises of posture and performance. And, third, there are the neurofibroma burden complications [1] deriving from the consequences. One of the most important complications is *extensive small-vessel hemorrhage within the neurofibroma*, either spontaneously or associated with surgery, whether intra-operative or in the day or so after the surgery [8]. This consideration not withstanding, I wish to encourage the approach of minimizing the amount of NF1 neurofibroma tissue in the first place, *focusing on the NF1 neurofibroma burden as a feature* in contrast to focusing on NF1 neurofibroma burden consequences and complications.

But, just what is meant by "neurofibroma burden?" I want to be very specific, because, as above, this phrase is one of the keys to NF1 morbidity and mortality. The kinds of verbiage and logic used here require refinement as we proceed to more successful treatment of NF1 neurofibromas. As a start, we need to consider both qualitative and quantitative aspects, for example, positron emission tomography (PET) [27] and tumor surface area [28-30] and volumetrics [26]. And along the way we need to consider NF1 neurofibromas and their associated problems with respect to whether they are being regarded as *features, consequences or complications*. Is the element merely present as a feature or are there also derivative elements, that is, consequences and/or complications? This set of considerations requires recognition that neurofibromas are not all the same, both intrinsically and as a function of time (progression) [31]. I consider that *there are three fundamental NF1 neurofibroma types* different from each other in certain critical ways [31]. A fourth type of neurofibroma is actually not a feature, but a consequence derived from epineurial or perineurial neurofibromas (see below), namely, *atypical neurofibromas* [27, 32-35]. The latter are also designated STEP lesions: **S**uspicious **T**umor **E**nlargement with **P**ET-scan positivity [27].

At least three types of NF1 neurofibromas (i.e., neurofibroma features) are necessary to account for the different combinations of their respective consequences and complications. This conclusion is abetted by the already-established trio of NF1 neurofibroma histopathological types: *Endoneurial, Epineurial* and *Perineurial* [31]. This nomenclature or classification keys off components of the nerve sheath that participate in lesion's formation and progression, namely, the epineurium, perineurium and endoneurium (Table 1).

Endoneurial neurofibromas initially derive from nerve sheath components available from the endoneurium at the termini of cutaneous sensory nerves – Schwann cells, fibroblasts, endothelial cells, pericytes and mast cells. Lymphocytes, adipocytes, perineurial cells and glandular cells may later be present as the neurofibroma enlarges and engulfs adjacent cells. Hair follicles and hair shafts may also be present on that basis, although sometimes bristles may be present

at the lesion's edges, apparently intrinsic to the neurofibroma.

Table 1. Neurofibroma Burden (Features, *Consequences* and Complications)

***Cutaneous (endoneurial) neurofibromas* (CN)**
Total number - dozens to many hundreds
Sizes - several mm to many cm; several mg to many Kg
Location – anywhere on the skin and mucous membranes
Regional density - especially midline of the back (lumbar, lower thoracic)
Flat, Sessile, Pedunculated, Involuted
Post-traumatic
Comfort/Performance influence - posture, position
Itching-Pain-Tenderness
Suckling - female areolae, nipples
Cosmesis - face, hands and forearms, external genitalia
***Diffuse plexiform (epineurial) neurofibromas* (DPN)**
Total number – one or several
Sizes – small to massive
Location – proximal or distal, internal and/or external; frequently ganglionic
Comfort/Performance influence
Regional encroachment
Itching-Pain-Tenderness
Malignant transformation
Neuronopathic
Cosmesis
***Nodular plexiform (perineurial) neurofibromas* (NPN)**
Total number – few to (frequently) many
Sizes – small to very large
Location – often, but not exclusively paraspinal
Malignant transformation
Comfort/Performance influence
Regional encroachment
Itching-Pain-Tenderness
Neuronopathic
Cosmesis
***Subcutaneous (perineurial) neurofibromas* (SC)**
Total number – moderate to many
Sizes – several mm to many cm
Location – anywhere along the length of a (sensory) nerve
Comfort/Performance influence
Regional encroachment
Itching-Pain-Tenderness
Malignant transformation
Neuronopathic
Cosmesis
***"Atypical" neurofibromas (STEP lesions)* (AN)**
Total number – one or few
Sizes – medium to large
Location – almost always in an established DPN, NPN or SN
Comfort/Performance influence
Regional encroachment
Itching-Pain-Tenderness
Malignant transformation

The amount of extracellular matrix (ECM) is highly variable. Recent localized trauma may herald the endoneurial neurofibroma's initiation [7,8]. Although specific measurements have not been made, I would expect that the endoneurial neurofibroma's internal temperature is chronically, if not constantly less than the normal physiological 37o C, especially when the endoneurial neurofibroma is pedunculated (Figure 3-5[36]). It is reasonable to speculate that this is a factor contributing to the lack of endoneurial neurofibroma malignant transformation. (Consider that a cryptorchid testicle may experience malignant transformation, presumably reflecting *merely* the transplanted tissue's resulting increase in temperature to 37^{o} C.) We also refer to endoneurial neurofibromas as *Cutaneous Neurofibromas* (CN) [31].

Epineurial neurofibromas are characterized by their initially having an epineurial outer limit, in stark contrast to endoneurial neurofibromas, and the epineurial sheath persists at least until the neurofibroma invades adjacent tissue, necessarily obliterating portions of the epineurial component. Epineurial neurofibromas are usually considered as arising from anywhere along a (sensory) nerve's length, including the nerve root, associated ganglia (especially the dorsal root ganglion [DRG]), nerve plexuses and various branches of the peripheral nerve itself. In addition to the components noted for the endoneurial neurofibroma, there may also be portions of "intact" perineurium or dissociated perineurial cells, and/or superficial hyperpigmentation (hyperpigmentation overlying a plexiform neurofibroma [HOPN]). Like the endoneurial neurofibroma, the amount and distribution of ECM is highly variable in amount and densaity, both from one lesion to another and within a "single" lesion. Epineurial neurofibromas are congenital lesions (see below), with peak periods of growth in the NF1 patient's first three decades. With the exception of Trigeminal epineurial neurofibromas, these lesions are susceptible to malignant transformation at least 15% of the time. (Is the Trigeminal DPN different in this manner because of its presumed lower intrinsic temperature?) Moreover, even while benign, epineurial neurofibromas can be very massive, weighing many kilograms [37]. We also refer to epineurial neurofibromas as *Diffuse Plexiform Neurofibromas* (DPN)[31].

Perineurial neurofibromas are characterized by an intact perineurium encompassing the entire lesion. The epineurium is intact as well. These latter two facts allow for blunt dissection of the lesions, allowing them and their involved nerves to be separated from adjacent tissues. (Generally, this is not possible for mature epineurial neurofibromas, i.e., DPN.) Perineurial neurofibromas appear to arise anywhere along the length of involved nerves, presumably their sensory components, from the paraspinal region to small distal branches. Specifically, ganglia, including dorsal root ganglia (DRG), appear *not* to be initiation sites [38], as they are for epineurial neurofibromas. The ECM variability is less prominent than for the other two NF1 neurofibroma types. When there are multiple perineurial neurofibromas in a nerve, the latter becomes distorted and tortuous, such that Von Recklinghausen dubbed them "Rankenneurom" (twisted neurofibromas). Not surprisingly, these taut lesions are often associated with substantial pain and tenderness. In general, NF1 patients who early on have a paraspinal perineurial neurofibroma at one site will eventually have them at multiple sites, at the extreme involving every spinal nerve root[39]. Perineurial neurofibromas of all sizes may present in the first five years of life, and they continue to initiate and grow for the rest of the NF1 patient's life. There is at least a 15% likelihood of malignant transformation for all such affected NF1 patients. We also refer to perineurial neurofibromas as *subcutaneous neurofibromas* (SN) or *nodular plexiform neurofibromas* (NPN)[31], the difference being primarily a function of size and location, with the SN being superficial and distal and the NPN being internal and proximal.

NF1 Congenital Diffuse Plexiform Neurofibromas

The NF1 DPN is a congenital mass lesion that initiates and begins maturing almost certainly under influences external to the NF1 fetus. At the least, the placenta regulates steroid hormone levels and other gene product levels and availability, including adrenomedullin and other neurotrophic factors [40, 41] and it is a major source of NGF [42]. Distinctive mast cells, critical elements of all NF1 neurofibromas, also characterize the placenta [43-45]. For these reasons, and likely others, considering a role for the placenta in both the intrauterine and postpartum progression of the DPN is cogent and compelling.

Unpublished data from an early 1980s collaboration I had with J.R. Perez-Polo[42- 46] involving three NF1 women, indicated that the amount of NGF in the NF1 placenta at term parturition is comparable to that in the placentas of women in the general population[47, 48]. These data are likely not the end of the story – there are also questions about critical time periods and target-tissue avidity for the NGF and about the placental origin and influences of other substances.

Often, at birth the DPN does not present as an obvious external mass, though there may be hyperpigmentation overlying the plexiform neurofibroma (HOPN), the latter often mistaken for a CLS. The HOPN coloration has a more orange tinge than a CLS and the edges are much more irregular, as in the photograph published in 1981[49] (by the way, the first color photograph published by the *New England Journal of Medicine*). The location of the HOPN is important: if it encroaches on the body's midline, involvement of the neuraxis (spinal cord, brain stem) is virtually certain. There may be associated hypertrichosis, often at the edges, the individual hairs resembling bristles. Moreover, the size of the DPN internally cannot be determined by the size of the HOPN.

At some time after birth, the surface of the DPN begins to enlarge, raising the lesion above the surface of the skin, sometimes leading to a massive lesion. For example, compare Figures 3-16. 4-16 and 4-17 in *Neurofibromatosis: Phenotype, Natural History and Pathogenesis* (2nd edition)[36], characterizing the progression of the lesion depicted in the 1981 photograph referenced above. Accompanying these anatomic changes, there may be lesion-localized pruritus (itching) and mild-moderate pain and tenderness. The DPN generally continues to enlarge throughout childhood and into and through the early adult years. As discussed above, surgery has been the standard treatment, though increasingly pharmaceutical approaches have been considered, both after the lesion is massive, and, alternatively, very early on so as to arrest or reverse progression[12]. For arrest, the emphasis has been on mast cell stabilizers, especially ketotifen [8,12,50-52].In this regard, one might query whether the potential adverse contribution of *placental mast cells* is compelling enough, and the frequency of congenital DPN is high enough, to warrant consideration of mast cell stabilizer treatment of a pregnancy involving an NF1-affected fetus.

The long term consequences of the congenital DPN include both massive overgrowth, with its associated problems (consequences and complications *sensu strictu*), and the minimum 15% likelihood of malignant transformation, most often to a neurofibrosarcoma [53-55]. Preventing this transformation may be one of the substantial results of the preempting and arresting effects of the mast cell stabilizing approach. However, this positive effect of ketotifen and similar drugs has yet to be investigated formally. I encourage that this be studied promptly. Why wait to treat after the "disaster," when the potential of avoiding it is tentatively at hand?

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