Case Report

Neurofibromatosis Type 1 and Polydactyly

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Keywords

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Abstract

Neurofibromatosis type 1 (NF1) is a neurocutaneous disorder that can impact the musculo-skeletal system. Polydactyly is not a commonly reported skeletal feature in NF1, but the presence of several case reports in the literature raises the question of an association. We report an individual with bilateral postaxial polydactyly of the feet diagnosed with NF1. To investigate whether these findings are coincidental or nonrandom, the prevalence of polydactyly in an NF1 research database and in other reported NF1 cohorts were compared to the prevalence of polydactyly in the general population. The previously documented cases of individuals with NF1 and polydactyly certainly provoke the question of a nonrandom association between these two findings. However, there are conflicting data from the previous reports that looked at the frequency of polydactyly in NF1 populations, and the data from our database point to a coincidental association rather than a nonrandom association. While several reports have suggested a potential mechanism for the co-occurrence of polydactyly and NF1, a concrete

association is still not yet well supported and caution should be used in attributing polydactyly to NF1.

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Introduction

Neurofibromatosis type 1 (NF1) is a neurocutaneous autosomal dominant disorder with an estimated prevalence worldwide of approximately 1 in 3,000 individuals [1]. NF1 is a condition with multisystem involvement and variable phenotypic expression. Clinical characteristics most commonly include cutaneous features (café au lait macules, freckling, neurofibromas), neurologic manifestations, ocular findings, and musculoskeletal features. The diagnosis of NF1 is typically based on the presence of specific cardinal clinical features that are relatively specific to NF1. A pathogenic variant in the *NF1* gene is detected in >95% of individuals showing clinical features of the condition [1]. However, there are less commonly reported and non-specific findings of NF1, such as renal artery stenosis, pulmonic stenosis, seizures, and various malignancies [2].

There is a range of abnormal musculoskeletal abnormalities in NF1, with some reporting an abnormality in approximately half of patients with NF1 [3]. Bone abnormalities reported to be associated with NF1 include scoliosis, osteopenia, vertebral dysplasia, sphenoid wing dysplasia, and bowing of the long bones. More distal congenital bone malformations, such as polydactyly, are not typically reported as a major phenotype of patients with NF1.

To date, there have been 5 published reports observing polydactyly in a total of 10 individuals with NF1 [4–8]. We present an additional individual with NF1 and bilateral, symmetrical postaxial polydactyly of the feet.

Case Report

This 3-year-old female was initially evaluated by medical genetics for numerous café au lait macules. She was born to a 34-year-old G5P4 mother at 35–36 weeks via normal spontaneous vaginal delivery after an uncomplicated pregnancy. The patient's father had a clinical diagnosis of NF1. An evaluation of the patient by an ophthalmologist was negative for Lisch nodules or signs of an optic glioma. Upon physical examination, the child was found to have >6 café au lait macules that were all >0.5 cm in size, in addition to axillary and groin freckling bilaterally. No neurofibromas were present. The growth parameters showed height in the 19th centile, weight in the 23rd centile, and head circumference in the 67th centile. Extremity assessment showed bilateral scarring on her feet from surgical treatment of polydactyly.

The patient was born with bilateral postaxial polydactyly type A of the feet (Fig. 1a, b) repaired in her first year of life with right and left flexor tenotomies with reconstruction of the lateral complex. Her preoperative radiographs showed five metatarsal bones bilaterally with postaxial polydactyly of the proximal, middle, and distal phalanges bilaterally (Fig. 1c, d). No other skeletal findings were present. At the time of her visit, the patient met clinical diagnostic criteria for NF1 based on her findings of >6 café au lait macules, axillary and groin freckling, and a first-degree relative with NF1.

Discussion

Polydactyly has both genetic and phenotypic heterogeneity and is one of the most common anomalies of the foot and hand. Polydactyly is classified into distinct categories based on the location of the duplication: postaxial (ulnar or lateral ray), preaxial (radial or medial), or central. It can be further distinguished by the level of skeletal duplication in addition to bilateral or unilateral involvement. The approximate prevalence of polydactyly is about 1.7 in 1,000 and ranges in the general population by ethnic background, sex, and type of polydactyly [9]. Postaxial polydactyly is the most common type, accounting for about 75% all of polydactyly cases, with an incidence in the African American population of 1 in 143 births and an incidence in the Caucasian population of 1 in 1,339 births [10, 11]. Alternatively, the incidence of preaxial polydactyly is about 1 in 3,000 births across all ethnicities [12]. Polydactyly can be part of a larger syndrome or, more commonly, observed in isolation. Polydactyly of the hand is slightly more common than polydactyly of the foot, and bilateral and unilateral polydactyly is seen approximately evenly [11].

In this report, we describe, as far as we are aware, the 11th individual reported in the literature with polydactyly associated with NF1. Table 1 outlines the specific type of polydactyly of our case and the 10 previously reported cases. Bilateral, postaxial polydactyly was most common among these individuals (5/10). Additionally, polydactyly evenly affected the hands and feet. The co-occurrence of polydactyly and NF1 previously reported in the literature may illustrate a nonrandom association [5–8], and some have proposed that there could be downstream effects of decreased neurofibromin on the Ras/MAPK pathway leading to this expanded phenotype [6, 8, 13, 14]. The Ras/MAPK pathway interacts with the FGF signaling pathway, which includes targets like sonic hedgehog (SHH), an important factor in bone formation and limb and digit development. In a recent case report, Kimes et al. [8] hypothesized that a deficiency of neurofibromin dysregulates the Ras/MAPK pathway, affecting downstream SHH targets and ultimately causing extra digit formation. Based on this hypothesis, Kimes et al. [8] proposed the consideration of broadening the clinical criteria for a diagnosis of NF1 in regard to the inclusion of polydactyly within osseous manifestations.

Several other reports also question a nonrandom association between polydactyly and NF1 given the commonality of other bone abnormalities seen in the condition. However, the consideration of coincidental findings is an important one. This is especially true given the relatively high prevalence of polydactyly in the general population and the prevalence of NF1 (1:3,000). It remains a reasonable possibility that polydactyly and NF1 are both independently occurring in the few reported individuals simultaneously by chance and are not manifestations of NF1. Several studies examined this phenomenon by looking at the frequency of coincidental findings on clinical exome sequencing. From these reports, up to 9% of patients received an incidental finding that indicates a high risk for another condition unrelated to and independent from the one they presented with, for which the test was indicated [15–20]. As these studies convey, these patients have two distinct diagnoses, which should not be mistaken for one condition with an expanded phenotype. This distinction, however, can be less obvious in cases in which patients are affected with multisystem disorders with many reported disease associations.

Conditions that affect multiple organ systems and present variably among affected individuals can pose a critical question in how to concretely distinguish coincidental findings from nonrandom associations of the underlying disease. This question has been introduced in the literature; for example, in manifestations of 22q11 deletion syndrome [21–23]. The features of 22q11 deletion syndrome vary widely and involve multiple systems. Several case reports of patients diagnosed with 22q11 syndrome propose novel phenotypes not typically seen in the affected population. Within these reports, some authors acknowledge that it is unknown if these features are directly related to the syndrome or merely coincidental finding; this is an especially difficult distinction given the variability within 22q11 deletion syndrome and its relatively high prevalence for a genetic condition. This discussion raises important concerns about the implications of widening a clinical picture of a condition based on single cases and small numbers. This is particularly important for genetic providers, as an expansion of a phenotype can affect counseling of the features and recurrence risks of specific phenotypic manifestations.

To better elucidate whether these published case reports of polydactyly and NF1 illustrate a mere coincidental finding or a more concrete association, we examined the prevalence of polydactyly in our own NF1 research database and in other reported NF1 cohorts. We compared these values to the aforementioned prevalence quoted in the general population.

We retrospectively reviewed our NF1 database comprising 281 individuals with NF1 enrolled in a research cohort for skeletal phenotyping. All individuals were examined by a single medical geneticist. Of the 281 individuals, only the abovementioned individual was reported to have any form of polydactyly. Hence, this does not dramatically support an increased prevalence of polydactyly in the NF1 population, but there are a limited number of individuals. In one case report, Shinawi and Patel [6] refer to the NF Foundation International database listing 7/4,051 (0.17%) individuals with NF1 with polydactyly. These numbers are not significantly increased compared to reports of prevalence rates of polydactyly in the general population [9]. However, in an earlier report, Ruggieri et al. [5] screened 135 individuals with NF1 evaluated at a neurofibromatosis clinic in Italy from 1990 to 1996. The frequency of polydactyly in this cohort was reported at 2.9%, which is relatively increased compared with the polydactyly prevalence in the general population. Interestingly, the authors quoted a frequency of polydactyly in their national population of 0.027%, much lower than other estimated frequencies of polydactyly in the general population [24].

The now 11 documented cases of individuals with NF1 and polydactyly certainly provoke the question of a nonrandom association between these two findings. However, there are conflicting data from the previous reports that looked at the frequency of polydactyly in NF1 populations. Although we add a single case of NF1 and polydactyly, when one takes into account the number of individuals with NF1 typically seen in a medical genetics clinic, it more likely is a coincidental association rather than a nonrandom association. While several reports have suggested a potential mechanism for the co-occurrence of polydactyly and NF1, a concrete association is still not yet well supported, and one should use caution in counseling families about potential associations that could distract from recognizing a second condition.

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Statement of Ethics

Informed consent for authorization to use and disclose health information for publication was obtained from the family and Institutional Review Board approval (#36259) was obtained.

Disclosure Statement

The authors have no conflicts of interest to declare.

Author Contributions

All authors contributed to the conception of the work, acquisition and interpretation of the phenotype, drafting or revision of the work for intellectual content, and final approval of the manuscript.

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Fig. 1. Footprints (**a**, **b**) of the patient's feet after birth with correlative radiographic images of the patient's feet showing postaxial polydactyly of the proximal, middle, and distal right (**c**) and left (**d**) phalanges.

Table 1. Review of reported patients with polydactyly and neurofibromatosis type 1

Year	Merlob et al. [4]			Ruggieri et al. [5]				Shinawi and Patel [6]	Shongo et al. [7]	Kimes et al. [8]	Current patient
	1987	1987	1987	1999	1999	1999	1999	2007	2015	2016	2016
Sex	M	M	M	F	M	F	M	M	F	M	F
Age, years	<1	5	adult	6	8	8	11	<1	14	37	3
Preaxial polydactyly	–	–	–	–	–	+(b)	+(b)	+(b)	–	+(u)	–
Postaxial polydactyly	+(b)	+(b)	+(b)	+(u)	+(b)	–	–	–	+(b)	–	+(b)
Site of polydactyly	f/h	f	f	h	h	f/h	h	f	h	h	f

(u), unilateral; (b), bilateral; f, foot; h, hand.