Scalp hair whorl patterns in patients affected by Neurofibromatosis Type 1: A case-control study

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ABSTRACT

Background: The hair whorl denotes the spiral disposition of hairs around an axis, which is determined by the follicle growing direction. Atypical variants of scalp hair patterns, identified by abnormally placed or multiple whorls, have been associated with early brain developmental disorders and several dysmorphic syndromes. Materials and Methods: A 6-month case–control, prospective monocentric study included an overall number of 557 children. A logistic regression analysis was performed to evaluate the relationship between localization, the number of scalp hair whorls, and their association with neurofibromatosis type 1 (NF1). Results: NF1 positively correlates with a frontal localization, whereas a negative association was found with a parietal whorl pattern (P < 0.001). Conclusion: Evaluation of scalp whorls gains importance in the neonatal settings and may contribute to suspect the early diagnosis of NF1, as the related National Institutes of Health diagnostic criteria cannot be usually observed at an early age.

Key words: Hair whorls, neurofibromatosis type 1, scalp pattern

INTRODUCTION

The term “hair whorl” describes the circular distribution of hairs on the scalp that revolves around an axis, which is determined by the follicle growing direction. Hair whorl patterns are characterized by the orientation or spin, the overall whorl number within the scalp, and the anatomical localization [Figure 1]. Among the many hypotheses done on their origin, most speculated the association between the hair whorls and central nervous system abnormalities. Familiar clusters have been reported in the literature, and a possible genetic linkage has been postulated. [1] The majority of the Caucasian population has a single apical scalp whorl, located in the parietal region underlying the vertex, either to the right of midline (56%), to the left (30%), or midline (14%). [2] The clockwise orientation is detected in 84% of the cases, while only 16% of hair whorls rotate counterclockwise. [3] Hair whorls’ features are still evaluated using the Ziering Classification. [4] In 2003, Furdon and Clark analyzed scalp whorl features distinguishing between Afro-Americans and Caucasians. [5] This distinction was necessary because a single apical whorl is detected in 95.5% of Caucasians, but only in 10% of African Americans, who present a double apical hair whorl in 90% of the cases. [6]

An anterior hair whorl, either clockwise or counterclockwise, is commonly found in trisomy 21 and Prader–Willi

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syndrome, while its association with microcephaly, Rubinstein–Taybi syndrome, and X-linked mental retardation remains anecdotal, being reported only in a few cases [Figure 2].[6,10-13] The coexistence of two or more hair whorls has been associated with mental retardation,[4] developmental and neurological disorders such as autism,[14] and epilepsy,[15] and it correlates with defects of cranial bones, including dicephaly and trigonocephaly [Figure 3].[6] Moreover, multiple hair whorls have been associated with facial dysmorphisms and inflammatory dermatological diseases such as guttate psoriasis.[16,17]

On the other hand, the lack of hair whorls had been related to microcephaly and encephalocele[10,14] even though it can occur in healthy individuals.[6]

In the clinical practice, hair whorls are often overlooked. Examining the hair whorl pattern, physicians should pay attention when a hair whorl pattern is not localized on the parietal region or when multiple whorls are present on the scalp. Based on the previous observations, atypical localization or an increased number in hair whorls does not necessarily imply any disease, since in healthy individuals, hair whorls with atypical localizations, spins, or numbers may be observed.[17]

The purpose of this study is to assess any possible association between hair whorl patterns and neurofibromatosis type 1 (NF1) in pediatric patients who have attended the dermatology clinic of Bologna University (Italy) during a period of 6 months.

**MATERIALS AND METHODS**

In a prospective monocentric observation study performed from September 2019 to the end of January 2020, we registered the number, spin, and location of hair whorls in children affected by NF1 (according to the diagnostic criteria as reported in the National Institutes of Health consensus development conference)[18] versus control pediatric patients affected by acute transitory skin conditions, and referred to the Emergency Unit of Pediatric Dermatology, at the Sant’Orsola-Malpighi University Hospital of Bologna during the same period. None of the controls had a genetic syndrome or inherited skin disease.

All patients were included after the parents had signed informed consent. In all patients, a detailed analysis of the scalp was performed. The hair whorl pattern was obtained by a different combination of three variable factors: whorl number, localization (parietal, frontal, and occipital area), and orientation (clockwise or counterclockwise).

An exclusion criterion was the impossibility to perform a correct assessment of the scalp hair pattern. Diseases characterized either by cicatricial or reversible hair loss, the presence of alopecia areata, or nonpathological
conditions such as the use of grooming techniques in patients with crinkled or very long hairs contraindicated patient recruitment.

The primary endpoint was to assess the frequency of scalp hair patterns in affected patients versus controls in the studied population. The second endpoint was to examine the possible association between a target whorl pattern and NF1.

For any hair whorl pattern, a statistical correlation of their frequencies among affected versus nonaffected participants, expressed as dichotomous variables, was analyzed by a binomial logistic regression. Proportions were estimated with 95% exact confidence interval, and statistical significance was assessed at $P < 5\%$ (0.05). All analyses were performed using IBM® SPSS® Statistics for Windows Version 23.0 (IBM Corp., Armonk, NY, USA). All examinations were performed in accordance with the Helsinki principles of medical ethics.

**RESULTS**

An overall number of 501 pediatric patients, all Caucasians, were included in the study and served as controls (median age: 11.22 years; standard deviation [SD]: 6.32, female/male ratio: 1.13). Controls' hair whorl patterns are reported in Table 1.

The reported clinical conditions were, in order of decreasing frequency: infective skin disorders (234/501, 46.7%), exogenous dermatitis (108/501, 21.6%), cutaneous burns (47/501, 9.4%), paraviral or postinfectious skin eruptions (43/501, 8.6%), urticaria and/or angioedema (38/501, 7.6%), exanthematous diseases (25/501, 5%), and adverse drug reactions (6/501, 1.2%).

Patients affected by NF1 were 56 (median age: 13.9; SD: 5.4, female/male ratio: 1.56). Positive family history for NF1 was reported in 37/56 cases. Hair whorl patterns in patients affected by NF1 are shown in Table 1.

The great majority of the controls showed a single hair whorl localized in the vertex area, with the hair oriented in a clockwise direction (352/501: 70.3%), while only 15.7% (76/501) of the patients had a single counterclockwise vertex whorl. Two scalp whorls were detected in 12.4% of the cases, with the parietal areas again been the most common localization. 66.1% of whorl duplets were co-localized within the same areas. The duplet spins were oriented both clockwise in 8 whorl pairs (19%), both counterclockwise in 2 cases (4.8%), or combined in a counterclockwise/clockwise pattern in the remaining 71.4% of the cases. A triple scalp whorl was very infrequent, being detected only in 9 patients. In none of these cases, the triplets were co-localized within the same areas and combined very heterogeneously.

The statistical analysis [Table 2] showed a positive correlation between the frontal hair whorl localization and NF1 was found ($P < 0.001$), whereas an inverse association between parietal location and NF1 was detected ($P < 0.001$).

| Hair whorls per patient | Number of patients | Hair whorl number, localization, and spin | Total whorl number |
|-------------------------|-------------------|----------------------------------------|-------------------|
|                         |                   | Parietal | Frontal | Occipital |                   |                   |
|                         |                   | CW | CCW | Both | CW | CCW | Both | CW | CCW | Both |
| Controls                |                   |   |     |     |   |     |     |     |     |     |
| Zero                    |                   | 2 | - | - | - | - | - | - | - | - |
| One                     |                   | 428 | 352 | 76 | - | - | - | - | - | - |
| Two                     |                   | 62 | 76 (8) | 25 (2) | - (30) | 5 | - | 12 | 6 | - (1) | 124 |
| Three                   |                   | 9 | 13 (3) | 6 | - (3) | 1 | - | 4 | 3 | - (2) | 27 |
| Total                   |                   | 501 | 441 (11) | 107 (2) | - (33) | 6 | 0 | 0 | 16 | 9 | - (3) | 579 |
| NF1 patients            |                   |                   |                   |                   |                   |                   |
| Zero                    |                   | - | - | - | - | - | - | - | - | - |
| One                     |                   | 47 | 38 | - | - | - | - | - | - | - |
| Two                     |                   | 8 | 9 (4) | 2 | - (1) | 1 | 1 | - | - | - |
| Three                   |                   | 3 | 1 | 1 | - (1) | 1 | - | - | - | - |
| Total                   |                   | 56 | 48 (1) | 3 | 2 | 12 | 1 | - | 2 | 2 | - |

Both cases and controls showed a single hair whorl (83.9% and 85.4%, respectively). Two scalp whorls were detected in 14.3% of the cases and in 12.4% of the controls, while a triple scalp whorl was very infrequent. The prevalence of frontal whorls was 4% and 9.4% in controls and NF1 patients, respectively. The mismatch between the number of patients and the total number of scalp whorls is due to the count of every single element in cases of multiple whorls. Double parentheses denote the features of whorl duplets that are co-localized on the scalp area of the same patient. None of the triplets are co-localized within the same scalp area in patients presenting with 3 hair whorls. NF1 – Neurofibromatosis type 1; CW – Clockwise; CCW – Counterclockwise.
A genetic factor conditioning scalp whorl patterning has been put forward in order to explain hair whorl formation in scalp areas lacking mechanical tension forces during embryogenesis. This theory has been validated by investigations based on the study of left-handedness, counterclockwise scalp whorls, and atypical right hemisphere location of the language center. Moreover, a metabolic etiology has been proposed. This theory supports the observation that hair follicles tend to be evenly spaced, suggesting that the activity of promoting and inhibiting growth factors conditions the distribution of the follicular units within the scalp. The hair whorl becomes the center of a decreased metabolic activity, due to the reduced release of morphogens.

Recent studies on mammals with hair whorls in the coat showed that the variation may arise from sequence variation in the genes involved in tissue polarity signaling, including Frizzled 6, a member of a large family of integral membrane Wnt receptors. The same system that patterns hair may also play a role in regulating the development of genetic brain anomalies.

Moore et al. studied the growth of the first hair coat in male mice administered with epidermal growth factor (EGF). The authors demonstrated that EGF plays a part in hair follicle development, and administering EGF in male mice caused hair whorl formation, resulting from the focal development of curved montrichs, characterized by reduced diameter and length. This finding becomes fascinating if tied to the ongoing debate concerning the EGF-receptor (EGF-R) role in Schwann cell tumor genesis, which is characteristic of NF1. An EGF-overexpressing genotype was associated with the early onset of NF1 clinical features. In addition, the EGF immunoreactivity was detected in week 15–16 fetuses at the level of surface epithelia. On the skin, the highest staining intensity was localized at the follicular ostia. The outer root sheath, and the Henle layer of inner root sheath above the papilla, showed both a positive immunoreaction. It is not clear how the EGF signaling pattern may condition the genesis of an abnormal whorl pattern; on the other hand, it is certain that this process is accomplished early, during the embryonic life.

By combining the different hypotheses upon the hair whorl formation, it is possible that the overexpression of EGF-R, already proved in NF1 murine tumor models, changes according to the different scalp areas. The EGF-driven metabolic response could trigger growth signals within the follicular units, altering their distribution and orientation.
in the scalp. However, the involvement of a mechanical component in the pathogenesis cannot be excluded.

The results of this study show that atypical frontal scalp hair whorls can be a premonitory sign of NF1, even though they can also be rarely detected in normal controls.

No significant association was found between double scalp whorls and NF1. The data in our series show a prevalence of double scalp whorls, the majority co-located in the parietal area, with 12.37% in controls and 14.28% in NF1 affected patients. The prevalence found in the control group is quite surprising since it is double that reported in the literature, which stands at 4.5%.\[7\]

The collected results showed a 1% (6/579) and 19.7% (12/66) prevalence of frontal hair whorls in controls and NF1 patients, respectively.

A previous study on 510 pediatric patients referred for dermatological consultations reported an overall prevalence of frontal whorls in 7.8%, which peaked at 17.14% in the subcohort affected by inherited skin disorders, without providing the accounted diseases.\[7\]

Smith and Gong characterized scalp whorl features in 200 Caucasian children, describing a 10% moderate out flare of the medial eyebrow patterning, and the anterior scalp hair upsweep in 7% of the patients, which does not imply the formation of a frontal hair whorl.\[11\] Anterior frontal whorls were reported to be associated with the cowlick pattern in 7% of the cases, which are located along the frontal hairline.\[8\]

CONCLUSION

In the literature, there is little evidence regarding aberrant scalp hair directional patterning in patients affected by NF1. Frontal hair whorl localization has been associated with NF1, but a focused case–control study is still lacking.\[7,28-30\] Evaluation of scalp whorls gains importance in the neonatal setting, as the National Institutes of Health diagnostic criteria for NF1 cannot usually be observed at an early age but develop later in life.\[18\]

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Conflicts of interests

There are no conflicts of interest.

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