

Study of the Demographic and Clinical Profile in a Neurocutaneous Rare Disease: A Cross-Sectional Study

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Abstract

Background : Neurofibromatosis is one of the most common dominantly inherited genetic disorders. The aim of this study was Study of the demographic and clinical profile in neurofibromatosis patient.

Methods : This study is cross-sectional conducted in 2020 on the population of patients with neurofibromatosis. Patients who are members of Neurofibromatosis Association answered the online demographic and clinical information questionnaire.

Results: 446 patients with neurofibromatosis participated in this study with a mean age of 33.39 ± 12.87 years. 297 patients (66.6%) were women and 378 (84.8%) patients had type 1 neurofibromatosis. The disease visibility was reported to be moderate in 254 patients (54.9%) and the severity of the disease was mild in 238 (53.4%) patients. The type of neurofibromatosis was not significantly related to gender, age groups, parental education, and ethnicity. The relationship between severity and age ($p = <0.001$) and gender ($p = 0.042$) was significant and the relationship between visibility and age ($p = <0.001$) was significant but despite the fact that the disease was more visible in men than women, it was not significantly related to gender.

Conclusions: The study results showed that the most common complication in the study population was *Café au lait* spot. In addition, visibility and severity of the disease were mild and moderate, respectively.

Background

Neurofibromatosis is a genetic disease of the central and peripheral nervous system that is inherited with a predominant autosomal pattern. The more common type of the disease, type 1 neurofibromatosis, occurs with a prevalence of one in every 3000 to 4000 births (1). Neurofibromatosis is the most common neurocutaneous syndrome. The disease is progressive and unpredictable, and its symptoms vary. The severity of symptoms may range from mild beauty damage to life-threatening conditions (2) .

The most common clinical manifestations in these patients are hyper-pigmented skin lesions (*Café au lait* spot), neurocutaneous neurofibromatosis, Lisch nodule, and learning difficulties. Optical gliomas and other malignancies and malignant tumors of the nerve sheath and bone lesions are also less common(3) .

Neurofibromatosis is a chronic disease and chronic and life-threatening diseases are among the most stressful factors in humans that affect a person's identity, psychosocial dimensions, emotional balance, self-satisfaction, sense of competence and efficiency, social interaction and interpersonal relationships. The individuals with chronic diseases should meet the challenges for achieving an acceptable level of health, physical, mental and social functioning (4). One of the psychological aspects of living with neurofibromatosis is a high level of concern about the condition and the unpredictable progression of the disease. Visible neurofibromatosis causes significant concern, especially in young women and low self-esteem (5). Low self-esteem and other psychological problems can be the result of childhood experiences

of learning disabilities and failure at school (6). About 20% of patients with skin diseases suffer from bad mood and 7% of patients suffer from depression and commit suicide (7). The patients with neurofibromatosis also have mental disorders, anxiety, personality disorders, depression, and suicide attempts (8). Cognitive impairment may persist into adulthood and affect a person's job performance, hence impairing the quality of life completely in patients with neurofibromatosis, especially in severe cases(9). The patients with neurofibromatosis are also at risk for various tumors and have a lower life expectancy than the general population of 10 years (10). Although skin lesions are the most significant manifestation of neurofibromatosis, there is a possibility of involvement of other organs and cancer (11). Due to the rarity and the prevalence of the disease in the country and the lack of a database (12) access to clinical information and demographics of neurofibromatosis helps to provide comprehensive care to patients with codified planning. Accordingly, the present study was conducted for the first time in the country with the aim of determining the demographic and clinical information of patients with neurofibromatosis in

Material And Methods

This cross-sectional study was conducted in 2020 in population patients with neurofibromatosis. Sampling method was non-random and convenience. 446 patients with neurofibromatosis with the study inclusion criteria participated in the study. The study inclusion criteria were suffering from neurofibromatosis. Regarding the rarity of neurofibromatosis and the unavailability of patients in coordination with the Neurofibromatosis Support Association, the questionnaires were designed online. The participants completed the questionnaire online through the website. The patients were asked to complete an online questionnaire form for other affected family members who were unable to fill out an online form. Data collection tools included demographic information collection forms with questions such as age, gender, education, occupation, ethnicity, and etc., and clinical information including disease type, common signs and symptoms of the disease, severity, and visibility of the disease. Informed consent was obtained from all participants regarding their participation in the research by expressing the purpose, nature and method of study. Participants were assured of the confidentiality of their information files. Percentage, frequency, mean, Chi Square test, Fisher test, Cramer V coefficient, and Kruskal-Wallis test were used to report demographic and clinical information. The data were analyzed using software SPSS version 24.

Results

The study was conducted on 446 patients with neurofibromatosis. The mean age was 33.39 years at confidence interval of 32.19 to 34.60. 297 (66.6%) patients were female. In all three types of disease, the majority of participants were women (NF1(69.8), NF2(66.7), SCHW(50)). The study results of demographic information of patients are as follows (Table 1).

The study population in 8 regions of the country is as follows: North 49 (11.1) patients, Northwest 16 (3.6) patients, Northeast 43 (9.8) patients, West 30 (6.8) patients, Central 236 (53.5) patients, Southwest

56 (12.7) patients, Southeast 9 (2) patients, South 2 (0.5) patients (Figure 1).

Parents of patients with neurofibromatosis often had Fars ethnicity and high school education level (Table 2).

Clinical information of neurofibromatosis patients showed that type 1 (84.8) is more common in the study population. The first symptoms are more pronounced in the abdomen. The disease severity was often mild (53.4) and visibility in most cases was moderate (54.9) (Table3).

The study results of common symptoms in patients with neurofibromatosis showed that the most common symptoms in patients with neurofibromatosis were *Café au lait* spot (95.5), neurocutaneous neurofibroma (86.3) and freckles (78.3) (Table 4).

No significant relationship was found between type of neurofibromatosis with gender and age ($p = 0.743$) ($p = 0.593$). The distribution of the type of disease with gender and age is shown in Table 5.

In order to determine the relationship between the number of patients with the disease in the family and the education of the parents, it was first determined that plots were not normalized using $p < 0.0001$, so using Kruskal-Wallis test no significant relationship was found between the number of patients in the family and the education of the parents (father education $p = 0.901$ and mother education $p = 0.507$).

Also, no significant relationship was found between ethnicity and type of disease using Fisher's exact test ($p = 0.191$).

A significant relationship was found between age and severity of disease using X^2 test ($p = <0.001$), so that the severity of the disease increases with age. Also, a significant relationship between the severity of the disease and gender ($p = <0.001$), so that Cramer V test coefficient was 0.136. The severity of the disease was higher in men than in women. No significant relationship was found between lesion visibility and gender using Ablon scale ($p = 0.445$). Also, a significant relationship was found between age and visibility of lesions using Ablon scale ($p = <0.001$) (Table6).

Discussion

Recording rare diseases is an important part of clinical research efforts aimed to further understand the clinical signs and demographics of rare diseases. Since the variety of clinical symptoms in patients with neurofibromatosis is high(13), the identification of predictors that affect health outcomes in patients with NF1 requires the gathering of a large number of individuals for clinical epidemiological research. Given that the study in ... has not yet examined demographic and clinical information of neurofibromatosis patients (12), the purpose of this study was to investigate demographic and clinical information of patients with neurofibromatosis in ... In this study, most of the participants had type 1 neurofibromatosis. In a study by Seidlin (2017), the highest percentage of patients had type 1, then type 2 and Schwannomatosis (14). The prevalence of type 1 neurofibromatosis in the world is expected to be one in every 3,000 births, the prevalence of type 2 neurofibromatosis is two out of every 30,000 births, and

prevalence of Schwannomatosis is 1 out of every 40,000 births(15, 16). Most of the participants in this study were women. In other studies, women were more involved in health-related research (17, 18). The most common clinical symptoms in the present study reported in 446 patients were Café au lait spot (95.5%), Neurofibroma (86.3%), freckles (78.3%), and pain (47.5%). In a study by Noble et al. (2007), Café au lait spot (99%), Freckles (90%), Neurofibroma (84%), Lisch nodule (70%), skeletal lesions (14%) and optic glioma (4%) were common, respectively (19), Ferner (2007) also reported that the most common symptoms in more than 99% of patients with neurofibromatosis were Café au lait spot and neurofibroma (20). Bata (2019) also repeated that 98% of patients had Café au lait spot as more common symptoms (21).

The disease visibility in the population participating in this study was moderate, which was consistent with the study results of Page (2006). In the present study, the severity of the disease was reported to be mild. In a study by Page (2006), the severity of the disease on 4-option Riccardi scale was minimum (34%); mild (26%); moderate (34%); severe (0.6%), which was minimal and moderate were the highest percentage of disease severity(22).

No significant relationship was found between gender and ethnicity with the type of disease. The results of other studies also show that neurofibromatosis affects all races and both males and females equally (23). No significant relationship was found between age and disease type, which was not consistent with a study by Seidlin et al. (2017) (14). Only 14.3% of patients underwent genetic testing. Neurofibromatosis is diagnosed through genetic testing or clinical signs (24). In a study by Mansouri et al. (2017), 39% of patients have undergone genetic test. The results of the present study showed that using Riccardi scale, the severity of the disease was significantly related to age and gender, and according to Ablon scale, to measure the visibility of the disease, it was not significantly related to gender, while with increasing age the visibility rate increased. In a study, Zvulunov et al. (2000) found no significant relationship between age and gender with the severity of the disease(25). The results of the present study were inconsistent with the study results of Wolkenstein (2001) in the relationship between age and gender with the severity of the disease, so that no relationship was found between age and gender with the severity of the disease (26). The reason for this difference could be the sample size participating in the study. The present study was conducted on 446 participants, while a study by Wolkenstein was conducted with the sample size of $n = 128$. Another reason could be the type of patients participating in the study by Wolkenstein conducted only on patients with neurofibromatosis type I, while in the present study patients with type 2 neurofibromatosis were also examined for Schwannomatosis (26). The study results of Duong et al. (2011) showed that a reduction in Café au lait spot and an increase in Neurofibroma were significantly associated with increasing age ($p < 0.001$). The reduction in Café au lait spot has been reported for the first time in this study with increasing age, while exacerbation of spots and masses occurs with increasing age and with maturity and pregnancy of patients(27). One of the limitations of the study is that some patients do not have access to the Internet as one of the study exclusion criteria. Regarding rarity of the disease and geographical distribution, data collection using online questionnaires was an inexpensive and convenient method.

Conclusion

The study results showed that the most common complication in the study population was *Café au lait* spot. In addition, visibility and severity of the disease were mild and moderate, respectively.

Declarations

Ethics approval and consent to participate

This study was approved by the ethical review boards at the authors' institution. Informed consent was obtained from all participants regarding their participation in the research by clarifying for them the purpose of the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors read and approved the final manuscript.

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Tables

Tble1: Demographic information of neurofibromatosis patients.

| Demographic information of patient | N(%) |
|---|-------------|
| Gender | |
| Male | 149(33.5) |
| Female | 296(66.5) |
| Age (years) | |
| 1-17 | 49(11.1) |
| 18-35 | 208(47.2) |
| 36-55 | 160(36.3) |
| >56 | 24(5.4) |
| Marital statuses | |
| Single | 282(38.7) |
| Married | 148(20.3) |
| Divorced | 16(2.2) |
| Job | |
| Worker | 37(8.3) |
| Employee | 65(14.6) |
| Freelance job | 70(15.7) |
| Housewife | 95(14.6) |
| Retired | 18(4) |
| Unemployed | 161(36.1) |

Table 2: Parental Demographic Information of Neurofibromatosis Patients

| Demographic information of Parents | | |
|---|--------------------|--------------------|
| Parental ethnicity | Father N(%) | Mather N(%) |
| Fars | 287(64.3) | 299(67) |
| Azary | 72(16.1) | 66(14.8) |
| kord | 28(6.3) | 27(6.1) |
| lor | 39(8.7) | 37(8.3) |
| other | 20(4.4) | 17(3.7) |
| Parental education | | |
| illiterate | 110(24.7) | 132(29.6) |
| Elementary | 135(30.3) | 126(28.3) |
| High school | 137(30.7) | 134(30) |
| Academic | 64(14.3) | 54(12.1) |

Table 3: Clinical information of patients with neurofibromatosis

| Clinical Information | N(%) |
|---|-------------|
| Type of neurofibromatosis | |
| NF1 | 378(84.8) |
| NF2 | 6(1.3) |
| SCHW | 4(0.9) |
| The first organ symptom appeared | |
| Face | 61(13.7) |
| Hand | 62(13.9) |
| Foot | 53(11.9) |
| Abdominal | 151(33.9) |
| Back | 98(22) |
| Head | 21(4.7) |
| Genetic testing | |
| Yes | 64(14.3) |
| No | 380(85.2) |
| Visibility (Ablon scale) | |
| Mild | 151(33.9) |
| Moderate | 254(54.9) |
| Severe | 50(11.2) |
| Severity (with Riccardi scale) | |
| Minimal | 54(12.1) |
| Mild | 238(53.4) |
| moderate | 114(25.6) |
| severe | 40(9) |

Table 4: Type and frequency of complications detected.

| Percentage and frequency of symptoms of the disease | YES | NO |
|---|------------|-----------|
| | N(%) | |
| Latte Cafe Stains | 426(95.5) | 20(4.5) |
| Freckles in the armpits or groin | 349(78.3) | 97(21.7) |
| Soft bumps on or under the skin (neurofibroma) | 385(86.3) | 61(13.7) |
| Tumors inside the body | 207(46.4) | 239(53.6) |
| Tumor inside the spine | 81(18.2) | 365(81.8) |
| Tumors inside the brain | 66(14.8) | 380(85.2) |
| Plexiglas masses form | 142(31.8) | 304(68.2) |
| Spinal Deviation (Sclerosis) | 74(16.6) | 372(83.4) |
| Soft bones (feet or hands) | 44(9.9) | 402(90.1) |
| Sloping hands and feet | 58(13) | 388(87) |
| Inability to learn (difficulty memorizing, or reading and writing) | 98(22) | 348(78) |
| Stains on the iris of the eye | 127(28.5) | 319(71.5) |
| Tumor on the optic nerve (optic glioma) | 48(10.8) | 398(89.2) |
| Small size / short stature | 106(23.8) | 340(76.2) |
| Body pain | 202(45.3) | 244(54.7) |
| Headache | 212(47.5) | 234(52.5) |
| seizer | 31(7) | 415(93) |
| Hearing loss | 62(13.9) | 384(86.1) |
| Deafness | 14(3.1) | 432(96.9) |
| Ringing in the ears | 110(24.7) | 336(75.3) |
| Balance problems and poor walking balance | 63(14.1) | 383(85.9) |
| Falling face | 55(12.3) | 391(87.7) |
| Blindness | 17(3.8) | 429(96.2) |
| Cataract (cataract) | 17(3.8) | 429(96.2) |
| Schwannomatosis tumor | 18(4) | 428(96) |

Table5 :Enrollment by type of NF with age and sex.

| Type of neurofibromatosis | | | | |
|----------------------------------|-----------|--------|--------|----------|
| gender | NF1 | NF2 | SCHW | Total |
| male | 114(96.6) | 2(1.7) | 2(1.7) | 118(100) |
| Female | 263(97.8) | 4(1.5) | 2(0.7) | 269(100) |
| Total | 377(97.4) | 6(1.6) | 4(1) | 387(100) |
| Fishers exact test: 0.743 | | | | |
| Age(year) | NF1 | NF2 | SCHW | Total |
| 1-17 | 42(100) | 0 | 0 | 42(100) |
| 18-35 | 172(96.6) | 5(2.8) | 1(0.6) | 178(100) |
| 36-55 | 141(97.2) | 1(0.7) | 3(2.1) | 145(100) |
| ≥56 | 19(100) | 0 | 0 | 19(100) |
| Total | 374(97.4) | 6(1.6) | 4(1) | 384(100) |
| Fishers exact test: 0.593 | | | | |

Table6:Enrollment by age and gender with severity and visibility.

| Riccardi scale | | | | | |
|---------------------------------|-----------|-----------|-----------|----------|----------|
| Age(year) | minimal | mild | moderate | severe | Total |
| 1-17 | 26(53.1) | 14(28.6) | 6(12.2) | 3(6.1) | 49(100) |
| 18-35 | 17(8.2) | 120(57.7) | 52(25) | 19(9.1) | 208(100) |
| 36-55 | 8(5) | 93(58.1) | 45(28.1) | 14(8.8) | 160(100) |
| ≥56 | 2(8.3) | 8(33.3) | 11(45.8) | 3(12.5) | 24(100) |
| Total | 53(12) | 235(53.3) | 114(25.9) | 39(8.8) | 441(100) |
| X²: <0.001 | | | | | |
| Cramers V: 0.268 | | | | | |
| gender | minimal | Mild | moderate | severe | Total |
| male | 21(14.1) | 68(45.6) | 40(26.8) | 20(13.4) | 149(100) |
| female | 33(11.1) | 170(57.2) | 74(24.9) | 20(6.7) | 297(100) |
| Total | 54(12.1) | 238(53.4) | 114(25.6) | 40(9) | 446(100) |
| X²: 0.042 | | | | | |
| Cramers V: 0.136 | | | | | |
| Ablonscale | | | | | |
| Gender | Mild | moderate | Severe | Total | |
| Male | 46(30.9) | 83(55.7) | 20(13.4) | 149(100) | |
| Female | 105(35.5) | 161(54.4) | 30(10.1) | 296(100) | |
| Total | 151(33.9) | 244(54.8) | 50(11.2) | 445(100) | |
| X²: 0.445 | | | | | |
| Age(year) | Mild | moderate | Severe | Total | |
| 1-17 | 37(75.5) | 10(20.4) | 2(4.1) | 49(100) | |
| 18-35 | 69(33.2) | 120(57.7) | 19(9.1) | 208(100) | |
| 36-55 | 40(25) | 101(63.1) | 19(11.9) | 160(100) | |
| ≥56 | 3(12.5) | 11(45.8) | 10(41.7) | 24(100) | |
| Total | 149(33.8) | 242(54.9) | 50(11.3) | 441(100) | |
| X²: <0.001 | | | | | |
| Cramers V: 0.278 | | | | | |

Figures

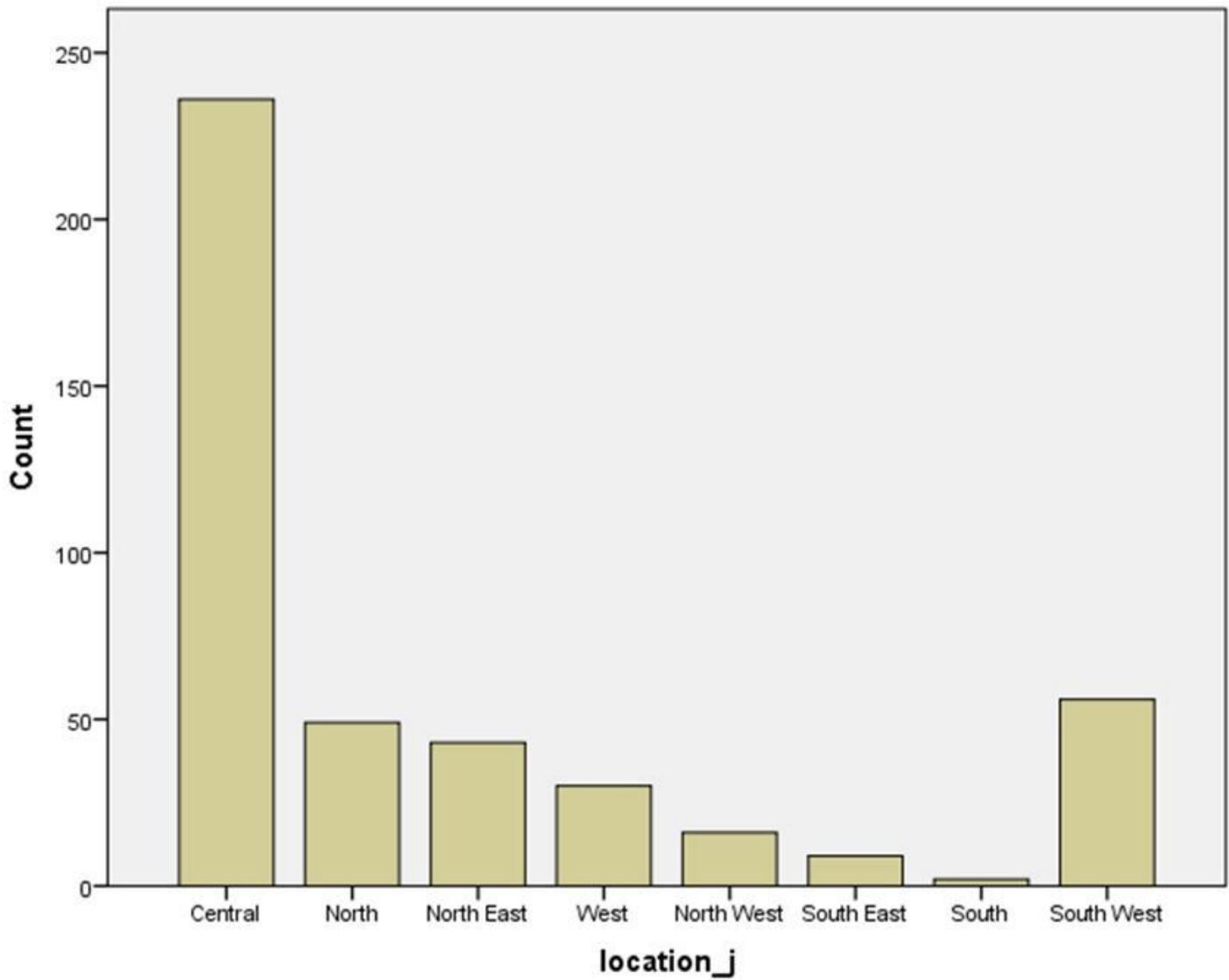


Figure 1

Study population in 8 regions of Iran.