

Is rheumatoid arthritis a neglected comorbidity in neurofibromatosis type 1?

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ABSTRACT

Aims: Neurofibromatosis type 1 (NF-1) is a relatively rare disorder with autosomal dominant inheritance. Despite current reports highlighting the association between NF-1 and some rheumatic diseases (e.g., systemic lupus erythematosus, juvenile idiopathic arthritis, ankylosing spondylitis, and antiphospholipid antibody syndrome), the literature seems to have missed focusing on its relationship with rheumatological disorders. Hence, the present study attempted to explore definite NF-1 molecular genetic mutation in association with accompanying rheumatic diseases, particularly rheumatoid arthritis.

Methods: The patients (n=23) aged 18 years who were diagnosed with NF-1 genetic mutation between 2010-2022 in the medical genetics department of our university were recruited for medical examination regarding rheumatic disorders in our rheumatology outpatient clinic.

Results: There were a total of 23 patients in this study, 14 (60.9%) males and 9 (39.1%) females, with a mean age of 27.4±9.2 years (18-51 years). As a result, 4 (17.3%) patients were diagnosed with rheumatoid arthritis (RA), 3 with seropositive RA, and one with seronegative RA. Of the diagnoses, two were established RA, and two were early RA. All patients with RA had a positive metacarpophalangeal joint (MCP) squeeze test and experienced pain in bilateral hands and wrists and morning stiffness for more than 45 min.

Conclusion: While the community prevalence of RA is about 1%, it is noteworthy that we detected RA in 17.3% of our patients. In the follow-up of patients with NF-1, routine examinations for pain in bilateral hands and wrists, morning stiffness over 45 minutes, and positivity of the MCP squeeze test are thought to allow early diagnosis of RA and, thus, relevant therapies.

Keywords: Neurofibromatosis type 1, arthritis, rheumatoid arthritis, autoimmune disease, joint

INTRODUCTION

NF encompasses NF type-1 (NF-1), NF-2, and schwannomatosis, which exhibit a range of clinically and genetically diverse characteristics. Accounting for about 90% of cases, NF-1 is detected in one in 3,000 live births regardless of sex. It has an autosomal dominant inheritance, but half of the patients often have a family history, while it develops due to de-nova mutations in the other half.¹ It was previously reported that the clinical diagnosis of NF-1 in about 95% of patients appears with a probable pathogenic variant.² The NF1 gene, located in the 11p12 region of chromosome 17, encodes a GTPase activating protein, a tumor suppressor protein called neurofibromin.³ Neurofibromin, on the other hand, is a negative regulator of the Ras-mitogen-activated protein

kinase signaling pathway, which regulates cell growth and proliferation. Therefore, inactivation of neurofibromin leads to hyperactivation of these pathway mediators and tumor formation.⁴

The most patent finding of NF-1 may be congenital café-au-lait spots. It is also accompanied by malignancies (e.g., lisch nodules, peripheral neurofibroma, optic glioma, brain stem gliomas, malignant peripheral nerve sheath tumors, leukemia, and gastrointestinal stromal tumors) and many other cardiovascular, orthopedic, and psychiatric comorbidities.^{5,6} In this sense, patients with NF-1 may need to be followed up in several medical departments (e.g., dermatology, general surgery, nephrology, endocrinology, neurology, physiotherapy,

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ophthalmology, orthopedics, and psychiatry), as NF-1 is directly and indirectly associated with many comorbidities 1, which makes patient follow-up and management challenging and leads to some disorder-related issues underestimated. In the literature, few case reports/series reported NF-1 to be coexistent with varied autoimmune disorders (e.g., multiple sclerosis, systemic lupus erythematosus (SLE), membranous glomerulonephritis, IgA nephropathy, mixed connective tissue disease, juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), antiphospholipid antibody syndrome (APS), autoimmune hemolytic anemia, bullous pemphigoid, vitiligo, and Graves' disease).⁷⁻¹¹

In our rheumatology practice, it was deemed a remarkable observation that three different NF-1 patients applied with complaints of pain and stiffness in their hands, and one patient was diagnosed with seropositive rheumatoid arthritis (RA). To date, only two case reports on the coexistence of NF-1 and RA have noted some interesting adverse reactions in NF-1 patients during RA treatment.^{12,13} Reckoning on our observations and previous research, we attempted to investigate the prevalence of RA and other rheumatological disorders that can be missed as lesser-known comorbidities in NF-1 patients.

METHODS

This study was approved by the Medical Faculty of Afyonkarahisar Health Sciences University Clinical Researches Ethics Committee (Date: 03.03.2023, Decision No: 2023/131). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Figure 1 presents a flowchart for inclusion criteria. We excluded those without an NF1 mutation in the molecular genetic analysis and under 18 years. While we recruited members of the same family who were followed up at our faculty, it was not the case for their non-followed-up relatives. Accordingly, we performed this study with 23 patients with a definite diagnosis of NF-1 in our tertiary center between January 2022-2023. The diagnosis of RA was decided upon the RA classification criteria proposed by the American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) in 2010.¹⁴ We diagnosed early RA and established RA according to the ACR Rheumatoid Arthritis Guidelines.¹⁵ According to this guide, if disease or symptom duration was <6 months, it was defined as early RA, and if ≥6 months, it was defined as established RA.

At the initial visits, we carefully performed anamnesis and physical examination of the patients and noted down symptom durations in symptomatic patients and arthritis patterns in those with arthritis (number, localization, and

distribution of affected joints). Moreover, we inquired all patients about the presence of rheumatological disorders or complaints in their relatives. Next, considering the patients' clinical findings, we ordered pertinent imaging tests, as well as laboratory tests for complete blood count (CBC) and biochemical profile, complete urinalysis, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and all autoantibodies including rheumatoid factor (RF; nephelometric, normal <14 IU/ml), anti-cyclic citrulline peptide (anti-CCP; ELISA, normal <17 U/ml). Blood samples were also studied for HLA-B27 and anti-nuclear antibody (ANA) (indirect immunofluorescence method, titration, and pattern), hepatitis B and C virus, and brucella (endemic to the research place). Moreover, the patients' complaints urged us to order radiographs of the hands, feet, sacroiliac joints, and the affected joints. We also performed ultrasonography (USG) in patients with arthritis and arthralgia in bilateral hands and wrists.

In this descriptive study, we recorded all the data in patient files and retrospectively analyzed the data in the hospital database. While presenting categorical variables as percentages and frequencies, we express continuous variables as means and standard deviations (range, min-max). All statistical analyses were performed on SPSS 26.0.

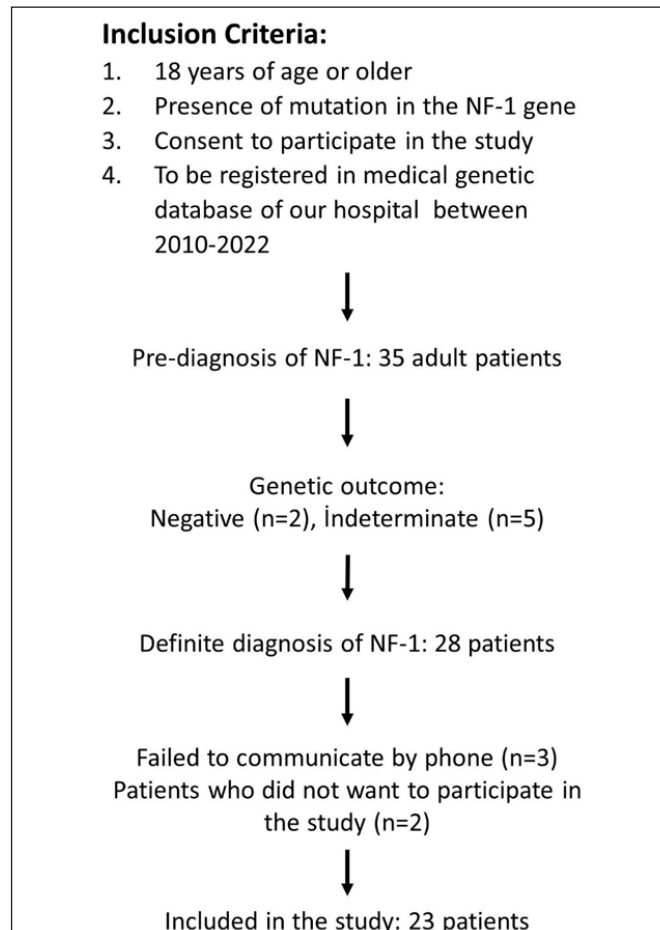


Figure 1. Inclusion flow diagram
Abbreviations: NF-1: Neurofibromatosis Type-1

RESULTS

There were a total of 23 patients in this study, 14 (60.9%) males and 9 (39.1%) females, with a mean age of 27.4±9.2 years (18-51 years). The patients' clinical and genetic characteristics pertinent to NF-1 are presented in **Table 1**. All patients had heterozygous mutations. The pedigree analysis showed no family history in only 2 (8.7%) patients, and they were considered to have a de-novo mutation. The cases recruited from the same family were Case 5 and Case 6 (siblings), Case 14 and Case 9 (siblings), Case 10 and Case 11 (mother-child), and Case-16, Case 18, and Case 20 (mother-two children) (**Supplementary Table**).

Sex; n (%)	
Male	14 (60.9%)
Female	9 (39.1%)
Age, years; M±SD (min-max)	27.5±9.2 (18-51)
Clinic features associated with the NF-1	
Family history of positivity; n (%)	21 (91.3%)
Café au lait; n (%)	23 (100%)
Neurofibroma; n (%)	9 (39.1%)
Lisch nodule; n (%)	2 (8.7%)
Epilepsy; n (%)	3 (13.0%)
Ataxic Gait; n (%)	1 (4.3%)
NF-1-associated genetic features †	
Pathogenic	12 (47.8%)
Likely pathogenic	10 (43.5%)
Uncertain significance (VUS)	1 (8.7%)

NF-1: Neurofibromatosis Type-1, VUS: Variant of uncertain significance
 † Mutations are considered "pathogenic, likely pathogenic, uncertain significance, likely benign, and benign" within the framework of the Mutation Classification defined by the American College of Medical Genetics.³¹

Table 2 displays the clinical and genetic characteristics of the patients with RA. Our first case, Case 3, had stiffness and pain in bilateral hands for about two hours in the mornings for 24 months and swelling in the last six months. In his physical examination, we discovered polyarthritis with symmetrical involvement of the proximal interphalangeal (PIF) joints of bilateral hands and arthralgias in both wrists and metacarpophalangeal (MCP) joints. Moreover, he had a positive bilateral MCP squeeze test. We also obtained the following laboratory findings: RF=129 IU/ml, anti-CCP=86 U/ml, sedimentation=49 mm/hr, and CRP 9.3 mg/dl. While the hand radiography showed periarticular osteoporosis and soft tissue swelling, the hand and wrist USG revealed joint capsule enlargement, synovial hypertrophy, and bone erosions on the joint surfaces in the metacarpophalangeal joints (**Figure 2**). The patient was diagnosed with seropositive RA upon the ACR/EULAR 2010 criteria.

Three out of four NF-1 patients with RA were males

Case ID	Sex	Age (years)	Complaints (Symptom duration)	Morning stiffness duration	Physical Examination Findings	MCP Squeeze Test	Laboratory findings†	Genetic features associated with the NF-1 ‡	NF-1 major findings and dysmorphic features	Another affected family member	Diagnosis
Case 3	Male	35	Pain and stiffness in bilateral hands (24 months)	120 min	Symmetrical polyarthritis of PIP and MCP joints of bilateral hands	Positive	ESR: 49 mm/h CRP: 9.3 mg/dl RF: 129 IU/ml Anti-CCP: 86 U/ml	NF1 c.1392+1G>T Likely pathogenic	Multiple café-au-lait spots, neurofibromas, facial dysmorphic features	2 daughters, 2 maternal uncles	Established seropositive RA
Case 9	Male	29	Pain, swelling, and stiffness in bilateral hands and wrists (12 months)	90 min	Arthritis of the 2nd and 3rd PIP joints of bilateral hands and wrists	Positive	ESR: 35 mm/h CRP: 11.2 mg/dl RF: 81 IU/ml Anti-CCP: negative	NF1 c.109_110delGA p.Glu37Alafs*29 Likely pathogenic	Multiple café-au-lait spots, neurofibromas, facial dysmorphic features	2 brothers, father, paternal grandmother	Established seropositive RA
Case 17	Male	44	Pain and stiffness in bilateral hands, wrists, and knees (5.5 months)	60 min	Arthritis in the 2nd, 4th, 5th PIP joints of bilateral hands and wrists. Arthralgia in bilateral knees	Positive	ESR: 29 mm/h CRP: 8.1 mg/dl RF: negative Anti-CCP: 102 U/ml	NF1 c.4537 C>T p.Arg1513X Pathogenic	Multiple café-au-lait spots, neurofibromas, rhabdomyosarcoma, Lisch nodules, facial dysmorphic features	Son, sibling, mother	Early seropositive RA
Case 22	Female	26	Pain and stiffness in bilateral wrists (5 months)	45 min	Arthritis in the right wrist. Arthralgia in right hand (2nd,4th PIPs), left hand (2nd,3rd PIPs), and left wrist.	Positive	ESR: 17 mm/h CRP: 6.2 mg/dl RF: negative Anti-CCP: negative	NF1c.3852_3854delAAT p.lle1284del CD147163 Pathogenic	Multiple café au lait spots	Mother	Early seronegative RA

MCP: Metacarpophalangeal; PIP: Proximal interphalangeal; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; RF: Rheumatoid factor (≥14 IU/ml positive); Anti-CCP: Anti-cyclic citrullinated peptide (≥17 U/ml positive); NF-1: Neurofibromatosis type-1; RA: Rheumatoid arthritis. † In addition to routine examinations, we performed tests for HLA-B27 and anti-nuclear antibody (ANA) (indirect immunofluorescence technique), hepatitis B and C, and brucella (endemic to the research place). ANA and HLA-B27 tests were negative in 4 patients with RA. ‡ Mutations are considered "pathogenic, likely pathogenic, uncertain significance, likely benign, and benign" within the framework of the Mutation Classification defined by the American College of Medical Genetics.³¹

Supplementary Table										
Case ID	Age	Gender	Mutation	ACMG classification	NF1 Major Findings	Dysmorphic Features	Zygoty	Is There Another Affected Individual?	Relationship Status	Laboratory Data
1	30	Man	NF1 c.2531 T>G p.L844R	Likely pathogenic	Multiple cafe au lait spots, neurofibromas, unilateral hearing loss	Long face, broad forehead, deeply set eyes, broad eyebrows, thick eyebrows, long palpebral fissures, prominent antitragus, long ears, narrow nasal bridge, fullness paranasal tissue, deep philtrum, exaggerated Cupid's Bow	Heterozygous	Aunt	None	No significant positivity in laboratory data
2	30	Man	NF1 c.2990+5 G>A	Pathogenic	Multiple cafe au lait spots	Long face, cheekbones prominence, broad chin, deeply set eyes, narrow nasal ridge, deep philtrum, exaggerated Cupid's Bow, thin lower lip vermillion	Heterozygous	Father	None	No significant positivity in laboratory data
3-RA	35	Man	NF1 c.1392+1G>T	Likely pathogenic	Multiple cafe au lait spots, neurofibromas	Brachycephaly, frontal balding, long face, prominence cheekbones, long chin, deeply set eyes, hypotelorism, sparse eyebrow, prominent antitragus, thick ala nasi, low insertion columella, narrow nasal bridge, smooth philtrum	Heterozygous	2 daughter, 2 maternal uncle	None	ESR: 49 mm/h; CRP: 9.3 mg/dl; RF: 129 IU/ml; Anti-CCP: 86 IU/ml
4	43	Man	NF1 c.6955 C>T p.Q2319*	Pathogenic	Multiple cafe au lait spots, neurofibromas	Long face, malar flattening, prominent nasolabial fold, broad chin, deeply set eyes, thick eyebrows, telecanthus, enlarged nares, wide nasal base, wide nasal bridge, deep philtrum, exaggerated Cupid's Bow, thin lower lip vermillion	Heterozygous	Mother, 1 sibling	None	No significant positivity in laboratory data
5	19	Man	NF1 c.910 C>T p.R304*	Pathogenic	Multiple cafe au lait spots, seizure, neurodevelopmental delay, lisch nodules	Malar flattening, thick eyebrows, telecanthus, thick ala nasis, bulbous nose, long philtrum, thick lower lip vermillion, thick upper lip vermillion	Heterozygous	Father, grandfather, uncle	Sibling with case 6	No significant positivity in laboratory data
6	37	Man	NF1 c.910 C>T p.R304*	Pathogenic	Multiple cafe au lait spots, neurofibromas	Long face, narrow face, prominence cheekbone, tall chin, thick eyebrows, low hanging columella, wide nasal base, thick upper lip vermillion, thick lower lip vermillion	Heterozygous	Father, grandfather, uncle	Sibling with case 5	No significant positivity in laboratory data
7	51	Woman	NF1 c.4084C>T p.R1362*	Pathogenic	Multiple cafe au lait spots, neurofibromas, sarcoma excision from arm	Long face, cheekbones prominence, malar flattening, broad chin, tall chin, deeply set eyes, downslanted palpebral fissures, high insertion columella, malaligned philtral ridges	Heterozygous	1 daughter, 1 son and maternal grandmother	None	No significant positivity in laboratory data
8	18	Man	NF1 c.6772C>T p.R2258*	Pathogenic	Multiple cafe au lait spots, ataxic gait	Malar prominence, deeply set eyes, sparse eyebrows, infraorbital creases, upslanted palpebral fissures, ptosis, thick ala nasi, wide nasal bridge, wide nasal ridge, deep philtrum, exaggerated Cupid's Bow	Heterozygous	2 brother, maternal uncle, maternal grandmother	None	No significant positivity in laboratory data
9-RA	30	Man	NF1 c.109_110delGA p.Glu37Alafs*29	Likely pathogenic	Multiple cafe au lait spots, neurofibromas	Full cheeks, midface prominence, tall chin, downslanted palpebral fissures, wide nasal base, thick lower vermillion	Heterozygous	2 brother, paternal grandmother	Sibling with case 14	ESR: 49 mm/h; CRP: 9.3 mg/dl; RF: 129 IU/ml; Anti-CCP: 86 IU/ml

Supplementary Table										
Case ID	Age	Gender	Mutation	ACMG classification	NF1 Major Findings	Dysmorphic Features	Zygoty	Is There Another Affected Individual?	Relationship Status	Laboratory Data
10	46	Woman	NF1 c.1541_1542delAG p.Q514Rfs*43	Pathogenic	Multiple cafe au lait spots	Broad chin, tall chin, smooth philtrum, thin lower lip vermillion	Heterozygous	1 son	Mother of case 11	No significant positivity in laboratory data
11	21	Man	NF1 c.1541_1542delAG p.Q514Rfs*43	Pathogenic	Multiple cafe au lait spots, short stature	Midface prominence, pointed chin, tall chin, wide spaced eyes, upslanted palpebral fissures, telecanthus, overfolded helix, narrow nasal ridge, exaggerated Cupid's Bow	Heterozygous	Mother	Son of case 10	No significant positivity in laboratory data
12	21	Man	NF1 c.499_502delITGTT p.C167fs10	VUS	Multiple cafe au lait spots, Macrocephaly, Regressive autism	Regressive autism	Heterozygous	1 cousin	None	No significant positivity in laboratory data
13	18	Woman	NF1 c.5439dupA p.Q18113fs*27	Likely pathogenic	Multiple cafe au lait spots	No features	Heterozygous	De Novo	None	No significant positivity in laboratory data
14	23	Man	NF1 c.109_110delGA p.Glu37Alafs*29	Likely pathogenic	Multiple cafe au lait spots, neurofibromas	Triangular face, full cheeks, midface prominence, pointed chin, downslanted palpebral fissures, wide nasal base, thick lower vermillion	Heterozygous	2 brother, father, paternal grandmother	Sibling with case 9	No significant positivity in laboratory data
15	19	Woman	NF1 c.1655_1657delTTC	Pathogenic	Multiple cafe au lait spots	No features	Heterozygous	De Novo	None	No significant positivity in laboratory data
16	45	Woman	NF1 c.5675delA p.K189fs*12	Likely pathogenic	Multiple cafe au lait spots	No features	Heterozygous	2 daughter	Mother of Case 18 and Case 20	No significant positivity in laboratory data
17-RA	44	Man	NF1 c.4537 C>T p.Arg1513X	Pathogenic	Multiple cafe au lait spots, neurofibromas, rhabdomyosarcoma, lisch nodules	Prominent supraorbital ridges, cheekbones prominence, deeply set eyes, prominent antihelix stems, protruding ears, macrotia, low insertion columella	Heterozygous	Son, sibling, mother	None	ESR: 29 mm/h; CRP: 8.1 mg/dl; RF: negative; Anti-CCP: 102 IU/ml
18	20	Woman	NF1 c.5675delA p.K189fs*12	Likely pathogenic	Multiple cafe au lait spots, Epilepsy	No features	Heterozygous	Mother, 1 sibling	Case 16's daughter, Case 20's sister	No significant positivity in laboratory data
19	29	Man	NF1 c.1541_1542del (p.Gln514fs)	Pathogenic	Multiple cafe au lait spots, thousands of Neurofibromas	Painful Neurofibromas	Heterozygous	Mother and 1 sibling	None	No significant positivity in laboratory data
20	19	Woman	NF1 c.5675delA p.K189fs*12	Likely pathogenic	Multiple cafe au lait spots, seizure	No features	Heterozygous	Mother and 1 sibling	Case 16's daughter, Case 18's sister	HLA-B27 positivity; no clinical signs of spondyloarthropathy
21	23	Man	NF1 c.3011_3011delA N1004Ifs*8	Likely pathogenic	Multiple cafe au lait spots, developmental delay	Broad forehead, short chin, prominent antihelix stem, serpinginous antihelix stem, wide nasal base, wide mouth	Heterozygous	Father, paternal uncle, paternal grandmother	None	No significant positivity in laboratory data
22-RA	26	Woman	NF1 c.3852_3854delAAT p.Ile1284del CD147163	Pathogenic	Multiple cafe au lait spots	No features	Heterozygous	Mother	None	ESR: 17 mm/h; CRP: 6.2 mg/dl; RF: negative; Anti-CCP: negative
23	30	Woman	NF1 c.2023_2034 insC	Likely pathogenic	Multiple cafe au lait spots	No features	Heterozygous	Mother	None	ANA positive in a dense fine mottled pattern at a titer of 1/80. Anti DFS-70 was positive. No clinical findings

*The patients in the blue filled row were diagnosed with rheumatoid arthritis.

aged between 26-44 years. All of them had stiffness in bilateral hands and wrist joints in the mornings for over 45 minutes and arthritis and/or arthralgia in bilateral hands and/or wrists. Then, we decided on seropositive RA for three patients (75%) and seronegative RA for 1 (25%). While two had established RA (50%), the other two were diagnosed with early RA (50%). Besides, we could not detect intra-articular neurofibroma in the ultrasonographic examination of any patient with RA (Figure 2).

All patients diagnosed with RA, except for Case 22, had neurofibromas accompanying café-au-lait spots and dysmorphic facial features. Unlike the others, we detected lish nodules and rhabdomyosarcoma in Case 17 (Supplementary Table). Yet, none of the patients with RA had a de-novo mutation, and their relatives did not have a history of any concomitant rheumatic disorder. RA Despite diagnosing Case 9 with RA, it was not the case for his 23-year-old brother, Case 14.

In the 30-year-old female patient (Case 23), the ANA by the indirect immunofluorescence technique was positive at a titer of 1/80 with a dense fine-spotted pattern. Anti-

DFS-70 also was positive in the immunoblot test. She had no features of connective tissue disease. Yet, our 19-year-old female patient had HLA-B27 positivity and no clinical signs of spondyloarthropathy.

Case-22 commenced hydroxychloroquine treatment since preparing for pregnancy. We started methotrexate treatment in the other three patients with RA due to the absence of contraindications. In addition, the patients were started on low-dose steroid bridge therapy and underwent tapering. No adverse effects were encountered in these patients, with a follow-up period of 3 months to 1 year until January 2023. Since being rhabdomyosarcoma in remission, Case 17 has been followed closely in the medical oncology department.

DISCUSSION

To date, diverse hypotheses have been proposed regarding an unusual aspect of NF-1, susceptibility to autoimmunity. Since neurofibromin is involved in the development and regulation of T cells, lymphocytic proliferation develops as a consequence of unregulated reticuloendothelial system (RAS) activity in T cells in NF-1 patients.¹⁶

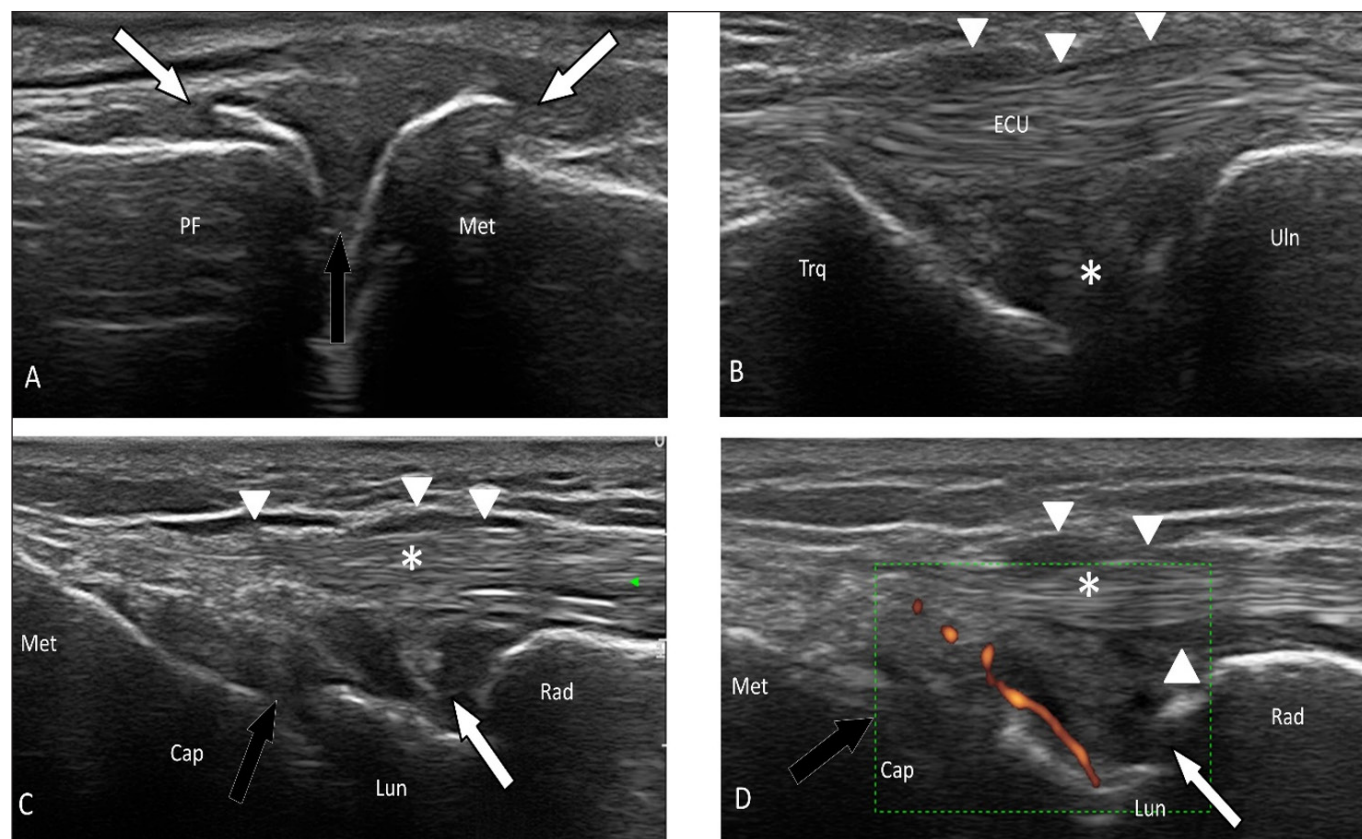


Figure 2. Ultrasonography findings of bilateral hands and wrists of patients with RA

Figure A (Case 3): Metacarpophalangeal joint (black arrow). Enlargement of the joint capsule, synovial hypertrophy, and bone erosions on the joint surfaces (white arrows).

Figure B (Case 9): Ulnocarpal joint (asterisk). Synovial hypertrophy and effusion in the joint space and tenosynovitis around the extensor carpi ulnaris (ECU) tendon (white arrowheads).

Figure C (Case 17): Radiocarpal joint (white arrow) and midcarpal joint (black arrow). Synovial hypertrophy and effusion in the joint space and tenosynovitis in the fourth compartment extensor tendon (white arrowheads). Asterisk: fourth extensor compartment tendon

Figure D (Case 22): Radiocarpal joint (white arrow) and midcarpal joint (black arrow). Increased Doppler activity in the joint space and tenosynovitis in the fourth compartment extensor tendon (White arrowheads). Asterisk: fourth extensor compartment tendon.

Abbreviations: Rad: Radius; Uln: Ulna; Lun: Lunate; Cap: Capitate; Met: Metacarpal; Trq: Triquetrum; PF: Proximal Phalanx.

Previously, loss of the immunosuppressive effect of neurofibromin was designated to be a possible hypothesis for the association of NF-1 with autoimmune anomalies. Moreover, mice studies on the link between neurofibromin deficiency and autoimmunity emphasized that immune dysregulation contributes to the development of myeloid leukemias, lymphoproliferative diseases, and autoimmune disorders.^{17,18} Another possible mechanism for autoimmunity involves free DNA released from proliferating cells and triggering an antigenic response. Thus, free DNA can be detected in NF-1 patients and systemic autoimmune diseases.^{19,20}

RA is known to be the most prevalent cause of chronic autoimmune inflammatory arthritis, developing as a result of the complex interactions of genes and environmental factors and ending up with an impaired immune tolerance and synovial inflammation in characteristic symmetrical joints.²¹ Besides, the literature host two interesting case reports pointing to the association of RA and NF-1. Despite being diagnosed with NF-1 at the age of 5, a 45-year-old female patient, who was followed up with additional seropositive RA for about 20 years and had no increased neurofibromas for the last 25 years, developed a diffuse cutaneous neurofibroma eruption on her arms, body, and face six weeks after tofacitinib 10 mg/day treatment. It was also reported in the study that cutaneous neurofibromas regressed within months following the discontinuation of tofacitinib treatment.¹² Tofacitinib is an inhibitor that inhibits the JAK3 pathway the most, and JAKs may also affect other signaling pathways through a process called intracellular crosstalk.²² Since tofacitinib potentially affects the RAS pathway through crosstalk, the same study speculated that it may have caused the development of diffuse neurofibromas in the patient without neurofibromas for 25 years.¹² Drago et al.¹³ reported that a 78-year-old female patient with RA developed dermatomal nodular with compatible histopathology with neurofibroma in the right thoracic region six months after infliximab treatment. The patient without a family history was considered segmental neurofibromatosis.¹³ As evident in the two cases above, it can confidently be asserted that anti-TNF and JAK inhibitors utilized in rheumatoid arthritis therapy may aggravate NF-1 findings or lead to atypical NF-1 clinics by affecting the pathways in the pathogenesis of NF-1. Therefore, these case reports specifically point to the possible unusual side effects of biologic drugs in the treatment of autoimmune diseases accompanying NF-1.

While the previous research often reports the prevalence of RA between 0.49% and 1% in Türkiye 23-25, we diagnosed 4 (17.3%) out of 23 NF-1 patients with RA. In this respect, this finding can be considered noteworthy for the relevant literature. Initiating RA treatment

immediately after the diagnosis seems critical to prevent long-term sequelae and complications.²⁶ Despite negative RF or anti-CCP antibodies in the early period of RA, about 80% of the patients have RF and/or anti-CCP positivity in the later stages. We were also able to diagnose 2 of the NF-1 patients with early-stage RA and 2 with established RA thanks to our awareness following our clinical observations, which may imply that rheumatological disorders can be overlooked in NF-1 patients. Even NF-1 follow-up guidelines do not often emphasize that rheumatological complaints should be questioned.²⁷ Therefore, our findings suggest that rheumatological complaints should also be explored in NF-1 follow-ups. Even without inflammatory arthritis, NF-1 patients may experience muscle and joint pain due to the nature of the disease. Plexiform, especially nodular neurofibromas, can cause joint pain if localized close to the joint area. Scoliosis, pseudoarthrosis, long bone dysplasia, and other bone lesions may also cause pain in patients with NF-1. In an NF-1 patient, it can be challenging to tell whether the pain is due to the nature of the disease or the development of RA.^{1,3,4} In these challenging situations, morning stiffness in the joints for more than 45 minutes and high CRP should warn clinicians about RA. Besides, since being a convenient, practical, and cheap technique, we recommend utilizing the MCP squeeze test as a RA screening technique.

In addition to RA, different inflammatory arthritis can be observed in patients with NF-1. For example, Till et al.⁸ reported a 3-year-old male patient presenting with monoarthritis in the right knee. What made this case stand out was that while the etiology of arthritis was being investigated, the patient was diagnosed with NF-1 upon noticing typical skin lesions.⁸ Gundogdu et al.⁹ reported a 43-year-old male patient with NF-1 who was diagnosed with AS due to inflammatory low back pain, HLA-B27 positivity, and bilateral grade 3/4 sacroiliitis findings on a sacroiliac radiograph.⁹ Despite HLA-B27 positivity in a 19-year-old female patient in our patient group, she had no significant clinical manifestation of spondyloarthritis. The prevalence of HLA-B27 in the general population is about 8%, and AS develops in only 1-2% of HLA-B27-positive patients.²⁸ It should also be noted that intra-articular neurofibromas are also involved in the differential diagnosis when an NF-1 patient presents with arthritis. In the case report by Saidane et al.²⁸ a 33-year-old female NF-1 patient suspected of septic sacroiliitis had articular plexiform neurofibromas in the juxta exhibiting extensive invasion of the right sacroiliac joint and soft tissue on magnetic resonance imaging.²⁹ Accepted as the prototype of autoimmune disorders in NF-1, SLE is often reported to be more prevalent than RA that it accompanies.³⁰ In our inquiry about SLE and other autoimmune connective tissue disorders, our patient

group had no clinical findings, such as a history of miscarriage or thrombosis, oral aphthae, photosensitivity, malar or discoid rash, alopecia, sicca symptoms, and Raynaud's phenomenon. Despite having ANA and Anti DFS-70 positivity, our 30-year-old female patient had no clinical features of autoimmune connective tissue disorder.

Our research delves into uncharted territory by investigating the prevalence of rheumatoid arthritis and other inflammatory rheumatic disorders in patients with NF-1. Nevertheless, a few limitations must be considered when interpreting the findings. The major drawbacks of this study may be its retrospective, single-center nature and relatively small sample size due to the rarity of the disease. It may, therefore, be challenging to generalize the findings to different populations.

CONCLUSION

Overall, we think RA prevalence in NF-1 patients may be higher than in the general population. In the follow-up of patients with NF-1, routine examinations for pain in bilateral hands and wrists, morning stiffness over 45 minutes, and positivity of the MCP squeeze test are thought to allow early diagnosis of RA and, thus, relevant therapies. It should also be noted that the presence of NF-1-related neoplasms and adverse reactions to be confronted during treatment may complicate the management of RA among these patients. Thus, there is a pressing need for more extensive research to gain deeper insights into the prevalence and relationship of RA among NF-1 patients, as well as safety data regarding the treatment of rheumatological conditions in this particular patient group.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Afyonkarahisar Health Sciences University Clinical Researches Ethics Committee (Date: 03.03.2023, Decision No: 2023/131).

Informed consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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