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Joint involvement in Noonan syndrome. A retrospective paediatric descriptive study

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Abstract:**Objectives:**

Noonan syndrome is a rare genetic disorder characterized mainly by congenital heart disease, occasional intellectual disability, and varied orthopaedic, rheumatological and haematologic anomalies. Despite potentially serious functional consequences, joint involvement has been rarely studied in the literature. Our objective was to perform a retrospective study evaluating the prevalence and characteristics of joint involvement in Noonan syndrome.

Methods:

We recorded articular symptoms, including their type and frequency, in patients with Noonan syndrome followed up in French hospitals. Patients were included if the diagnosis was confirmed before the age of 20 based on the van der Burgt criteria or genetic analysis. Data are presented as frequencies or medians (ranges), and patient groups were compared using chi-square or Fisher tests.

Results:

Seventy-one patients were included from 4 centres. The average age was 12.5 years (range: 2-36). Musculoskeletal pain was found in 18 patients (25%) and joint stiffness in 10 (14%) located in the wrists, elbows, ankles, knees and hips, which was usually bilateral. Only one destructive form was described (multiple villonodular synovitis and a giant cell lesion of the jaw). There were no cases of systemic lupus erythematosus (SLE) or other autoimmune arthritis. Raynaud's phenomenon was observed in 3 patients. Only 50% of joint complaints led to additional exploration. *SOS1* mutations ($P < 0.05$) and treatment with growth hormone (GH) ($P < 0.05$) were the only factors significantly related to musculoskeletal pain. Patients treated with GH did not have more *SOS1* mutations. Patients experiencing pain were not more likely to experience stiffness, joint hypermobility, or coagulation abnormalities.

Conclusion:

Joint manifestations were frequent in Noonan syndrome, predominant in large joints, and rarely explored. Multiple villonodular synovitis is characteristic but rare. Auto-immune disorders were not described in this cohort. A more multidisciplinary approach could be recommended for the early detection of possibly disabling rheumatologic manifestations.

Key words:

Joint involvement

Pigmented villonodular synovitis

Central giant cell granuloma

Noonan Syndrome

RASopathy

1. Introduction:

Noonan syndrome (NS) is a genetic disorder inherited in an autosomal dominant manner. The incidence of the syndrome has not been clearly defined: it might range from 1/1000 to 1/2500 live births according to Nora et al. (1). It is probably underestimated due to the great phenotypic variability.

Despite an initial clinical definition, NS has been classified as a RASopathy following the identification of various genetic mutations. These are gain-of-function germline mutations of genes involved in the RAS/MAP kinase pathway (2). A genetic abnormality can be found in 75 to 80% of cases (3). The most frequent mutations are heterozygous mutations in the *PTPN11* gene (50% of identified mutations) and the *SOS1* (15%) gene, but mutations in the *KRAS*, *RAF1*, *RIT1*, *NRAS*, *SHOC2*, *RRAS*, *CBL*, *SOS2*, *RASA2* and *LZTR1* genes have also been reported (2). The van der Burgt criteria (4) [Appendix A, Table S1; See the supplementary material associated with this article online] identify the main diagnostic elements, but the phenotype may differ greatly between patients. The phenotype evolves with age, and dysmorphism is more characteristic in children (Appendix A, Table S2).

The cardinal signs are craniofacial dysmorphism, cardiac malformations such as pulmonary stenosis or hypertrophic cardiomyopathy, and an average to short height (5).

Heterogeneous coagulation disorders are also present, which are predominantly platelet function disorders but also mild deficiency in factor VII, IX, or XI, low von Willebrand factor, and thrombocytopenia (6).

Musculoskeletal symptoms are heterogeneously reported in the literature and can involve joint swelling, musculoskeletal pain and skeletal deformities.

In regard to auto-immune conditions, Bader Meunier et al. proposed in 2013 a link between systemic lupus erythematous (SLE) and Noonan syndrome under the umbrella of monogenic SLE. However, these descriptions remain scarce. In the literature, 8 cases of SLE associated with NS have been described with polyarthritis (7/8 patients), immunological cytopenia (4/8 patients), pericarditis (4/8 patients), and a patient presenting skin lesions.

While they have not been assessed in large-scale studies, various orthopaedic anomalies are frequently reported. First, chest deformities, in particular superior pectus carinatum with a characteristic inferior pectus excavatum (30-70%) or widely spaced nipples, scoliokyphosis (30-60%), and cubitus valgus (45%) (7,8).

Joint stiffness has been reported, especially in the knees, elbows and hips. Pain in the back, legs, thighs, knees or feet has also been described. Small joint laxity and large joint contractures have been described in other RASopathies, such as cardiofaciocutaneous syndrome (CFC) and Costello syndrome (9,10).

Finally, several clinical cases have reported the association of multiple giant cell lesions (MGCLs) with NS. These affect mainly the patient's jaw or synovial joints (pigmented villonodular synovitis) and most commonly involve large joints (knees, hips, and ankles) (11–14). Coagulation disorders occur frequently in this population, and similarities exist between villonodular synovitis and haemophilic arthropathies (similar preferential location, thickening of the synovium, and haemosiderin deposits)(15,16). One might therefore wonder whether microbleeds could foster their development.

The spectrum of orthopaedic abnormalities in Noonan syndrome is thus broad. However, joint pain or stiffness have been scarcely described, and articular symptomatology is likely undervalued due to the severity of other aspects of the syndrome, especially cardiac involvement. Even so, these anomalies should not be neglected, as some of them can have important functional consequences, especially in children.

The aim of this study was thus to perform a retrospective multicentre study to evaluate the prevalence of joint pain in patients monitored by paediatric departments in French care centres and to describe their association with other manifestations of the syndrome.

2. Methods:

We performed a retrospective study based on the records of patients monitored by French paediatric departments. Data were collected from July to October 2019.

2.1. Patient selection

Patients were recruited by a nationwide call for observations sent through SOFREMIP (Société Francophone pour la Rhumatologie et les Maladies Inflammatoires en Pédiatrie), first to paediatric rheumatology centres and then to paediatric centres (patients are seldom followed by paediatric rheumatologists but rather by paediatric cardiologists and paediatric endocrinologists). To be included, patients had to present clinically (per the van der Burgt criteria) and/or genetically confirmed Noonan syndrome diagnosed before age 20. Patients suffering from RASopathies other than Noonan syndrome were not included in this study.

2.2. Evaluated parameters

We researched the frequency of pain described as joint pain, diffuse seemingly musculoskeletal limb pain, joint stiffness, swelling, coagulation balance abnormalities or other involvement related to Noonan syndrome. We compared groups with and without musculoskeletal pain (defined as joint pain or diffuse musculoskeletal limb pain) and with or without joint stiffness.

2.3. Ethics Approval and consent to Participate

The NOORHA study (29BRC19.0101) was approved by the ethics committee « Comité d'éthique de Brest » (B2019CE.23/1) on February 25, 2019. Data were collected with a standardized questionnaire after the patient's consent had been obtained.

2.4. Statistical analysis

Since some of the patients included had missing data (10%), the denominator varied across variables. All percentages were calculated based on the number of patients for whom the variables were available. Data are presented either as frequencies or as the median (range) according to their distribution. The chi-square test (or Fisher's exact test where appropriate) was used to compare groups. P values less than 0.05 were considered significant.

3. Results

3.1. Patients characteristics (Table 1)

A total of 71 patients were included from 4 centres: 27 girls (38%) and 44 boys (62%) were enrolled, and the average age was 12,5 years (range: 2-36). All patients were diagnosed before age 20 ; among them, 18 were diagnosed before 6 months of age (25%). Thirteen of 71 patients (18%) had a known or suspected family history of NS.

NS diagnosis was based on the van der Burgt criteria for 80% of the patients (52/65). For the other patients in the study, the diagnosis was confirmed genetically on the basis of a suggestive clinical presentation. In our population, 92% (66/71) of patients presented a genetic abnormality, mainly in the PTPN11 and SOS1 genes.

A total of 61/62 patients (98%) had compatible facial dysmorphology. A total of 40/69 patients (58%) were less than -2 standard deviation scores (SDSs) below the mean size, and 26/70 patients (37%) were treated with growth hormone.

Three patients had juvenile myelomocytic leukaemia.

3.2. Joint and musculoskeletal symptoms

Peripheral joint pain was described in 12/68 patients (18%). Ten patients had joint stiffness located in the wrists, elbows, ankles, knees and hips. Joint stiffness was usually bilateral except for one patient whose joint stiffness was posttraumatic. For 6/10 patients (60%), stiffness was not associated with pain. A limping was found in 3 patients (4%) due to stiffness in the knees. Diffuse lower limb pain was present in 9/68 patients (13%), and axial pain was rare (3/68, 4%). Diffuse upper body pain was not found in any of the studied patients (Figure 1).

Only one patient had multiple villonodular synovitis involving the wrists, elbows, ankles and knees as well as a giant cell lesion of the right mandibular ramus. Joint swelling associated with pain and stiffness of the wrists, elbows, and knees was described in this patient.

Thirteen patients (20%) had scoliosis, and 2 had spinal canal stenosis with a narrowing of the interpedicular distance of the lumbar spinal canal. In one of those patients, it was described a Klippel-Feil syndrome and a Noonan syndrome with SOS1 mutation.

Moderate hypermobility of large joints was found in 5 patients (18%). Hypermobility of small joints was found in 10 patients (38%). Skin hyperextensibility was described in 5 patients (7%).

There were no cases of systemic lupus in our study population; only 3 cases of Raynaud's phenomenon were identified with normal capillaroscopy, and for one of them, frostbite was observed.

The FAN was researched for only 3 patients: One patient having musculoskeletal symptoms whose had 1/160e without specificity. 2 others patients because of cutaneo-vascular acrosyndrome and were negative. The one with frostbite had anti-MPO ANCA.

Regarding coagulation disorders, 6 (9%) patients suffered from abnormal postoperative bleeding. There was no intra-articular bleeding. Thirty-six (55%) patients had minor bleeds (easy bruising of the lower limbs, epistaxis, gingivorrhagia, menorrhagia).

3.3. Comparison of patients with and without musculoskeletal pain (Table 2)

Musculoskeletal pain was not associated with any particular phenotype. However, joint pain was more frequent in patients with SOS1 mutations ($P < 0.05$).

Treatment with GH was significantly related to the occurrence of pain (16/26 vs 10/26, $P < 0.05$). Patients treated with GH did not carry more SOS1 mutations (2/25 treated patients vs 9/40 not treated, non significant).

Patients experiencing pain were not more likely to experience stiffness or hypermobility in small or large joints.

Patients with musculoskeletal pain were not more likely to experience abnormal postoperative bleeding, minor bleeding or abnormalities in coagulation balance. The patient with pigmented villonodular synovitis had minor bleeding without abnormal coagulation balance or factor deficiency.

Among the 18 patients with musculoskeletal pain, 13 (72%) underwent imaging: 9 underwent X-rays, 2 underwent ultrasonography, and 2 underwent MRI. All of them were referred to other experts: 7 had consulted an orthopaedic surgeon, 2 had a consultation with physical medicine and rehabilitation, 3 had a rheumatology consultation, and 6 had received physical therapy.

3.4. Comparison of patients with and without joint stiffness (Table 2)

Except in one patient diagnosed with villonodular synovitis, the stiff joints were not swollen. All patients with a limp also had joint stiffness ($P < 0.05$). No other association was statistically significant.

Of the 10 patients with stiffness, 3 received X-rays, 2 received an ultrasound and an MRI, 3 consulted an orthopaedic surgeon, 1 had a consultation with physical medicine and rehabilitation, 1 had had a rheumatology consultation, and 3 received physical therapy.

4. Discussion:

While it could affect patient quality of life, joint involvement in Noonan syndrome has rarely been studied in the literature. Most NS patients are diagnosed in childhood, and our study focused on musculoskeletal manifestations of NS. We studied the frequency of joint involvement (pain, stiffness, synovitis, villonodular synovitis and structural damage), the frequency of diffuse musculoskeletal pain and the frequency of major musculoskeletal dysmorphisms (pectus excavatum and small size).

This study enabled us to highlight the relatively high frequency of these involvements (in up to 25% of patients), mainly pain in the lower limbs and stiffness in the elbows, knees, ankles and hips. Patients with musculoskeletal pain were more often treated with GH (61%). Treatment with GH can induce articular and muscular pain. However, such side effects are dose-related and rare. They occur more frequently in the first months after the initiation or modification of treatment (17). However, in our study population, GH was probably not the only factor, as on the one hand, this pain lasted for several years, and on the other hand, 41% of patients with musculoskeletal pain were not treated with GH. Therefore, musculoskeletal pain is very likely related to NS itself. Other factors might be relevant, such as musculoskeletal particularities related to Noonan syndrome.

As already been observed in other RASopathies (9,10), stiffness affecting large joints with flexion deformity and joint hypermobility, especially in small joints, were both found in our study population. These abnormalities coexisted in 3 patients. Hypertonia and muscle contractures predominantly in large joints, mainly with short Achilles tendons, have also been described in the literature in cardiofaciocutaneous syndrome and Costello syndrome (9,10). It has been suggested that the higher occurrence of encephalopathies and strokes in these forms of RASopathies might partly explain these specific orthopaedic disorders (9,18), but this connection could not be made in our study population. It has also been suggested that laxity in some joints could lead to a compensatory contracture in other joints (such as that of the midfoot causing stiffness in the ankle in dorsiflexion with a short Achilles tendon) (8). No such relationship was found in our study population. They seem to have mostly mechanical joint involvements. Therefore it would be very interesting to have MRI for all the patients with stiffness to precise the lesions.

Multiple pigmented villonodular synovitis in Noonan syndrome can have a relatively pain-free symptomatology that is likely to cause a delay in diagnosis. Therefore, we deem it important that these children be referred to a rheumatologist in the course of their medical care. This is a very severe and challenging complication of NS. Concerning affected joints, they initially might not be swollen or slightly puffy (15). The arthralgia is mechanical (19,20), with a progressive decrease in joint mobility. The swelling may fluctuate (20,21). The intra-articular location could be the cause of mechanical symptoms, anterior knee pain, meniscal pain, and patellar dislocation (15,22). The knees, ankles, hips and elbows are primarily affected (14). At an early stage, these clinical features can easily be mistaken for the previously described musculoskeletal features. These involvements have high destructive potential, hence the importance of early diagnosis. Ultrasound can be recommended, as it is an easily accessible and radiation-free imaging technique, but MRI is the best examination technique to obtain an early diagnosis and early support.

Rheumatic auto-immune disorders were not described in this cohort but autoimmunity (especially ANA, dsDNA) were rarely explored. Due to the retrospective data, we have no information about the inflammatory status (ESR, CRP). Both would be very useful in the follow up for better classifying the musculoskeletal manifestations although the literature they are very rarely described (23). Three patients with Raynaud's phenomenon have been described with normal capillaroscopies. To the best of our knowledge, no association between acrosyndromes and Noonan syndrome has been suggested to date. It could be suggested to explore such cases for SLE.

Bleeding disorders are a major issue in Noonan syndrome. First, the existence of coagulation disorders may complicate the management of articular manifestations, and second, a significant proportion of these patients will require surgery. It is therefore important that these patients be screened and treated accordingly (24,25). A coagulation profile could not be obtained for all patients included in our study. Neither haemarthrosis nor links between haemostasis disorders and articular manifestations were found in our study population.

The limitations of the study were related to its non-exhaustiveness. It was an analysis involving 4 centres in France. Due to the retrospective record-based nature of this study, all data that had not initially been sought or transcribed by clinicians were not available. Moreover, most patients were followed in paediatric, cardiology, endocrinology or haematology units and had seldom been seen by a rheumatologist (6%), even when articular manifestations were reported (17% of patients with pain and 10% of patients with stiffness). A prospective study with a systematic rheumatological assessment might be of interest to accurately detect articular involvement, especially synovitic lesions. It must be recognized that these patients require a multidisciplinary approach involving orthopaedists, rheumatologists and rehabilitation specialists (24).

The evolution of musculoskeletal specificities associated with Noonan syndrome in adulthood is not known. Indeed, no long-term follow-up recommendations have been formulated. Once initial cardiological, endocrine and psychodevelopmental monitoring is complete, these patients are often lost to follow-up as they become adults. New studies will be necessary to better understand the natural history of the musculoskeletal anomalies and their evolution to supplement current recommendations and monitoring protocols.

Declarations:

Ethics Approval and Consent to Participate:

This study was approved by the B2019CE.23/3 ethics committee under the study code 29BRC19.0038 - NOORHA. All patients gave consent to use their data anonymously.

Consent for publication:

Not applicable

Competing interest: All authors have declared no conflicts of interest.

Author Contributions: ALQ, AS and VDP designed the study and analysed the data. ALQ, AP, SAB, KB, TE, CC, CO and SP performed the clinical data gathering. The final manuscript was read and approved by all authors.

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Table 1: Characteristics of the population.

| | <i>n</i> | % |
|-------------------------------------|----------|------------|
| Population | 71 | |
| Male | 44/71 | 62% |
| Age at inclusion | 2 - 36 | 12.5 ± 7.8 |
| Van der Burgt criteria | 52/65 | 80% |
| Compatible facial dysmorphology | 61/62 | 98% |
| Genetic mutations | 66/71 | 92% |
| <i>PTPN11</i> | 47/66 | 71% |
| <i>SOS1</i> | 11/66 | 17% |
| <i>RAF1</i> | 2/66 | 3% |
| <i>KRAS</i> | 3/66 | 4% |
| <i>BRAF</i> | 1/66 | 1% |
| <i>SHOC2</i> | 2/66 | 3% |
| Height | | |
| Less than -2 SDS | 40/69 | 58% |
| Treated with GH | 26/70 | 37% |
| Age at start of GH | 4 - 13 | 7.8 ± 3.2 |
| Coagulation disorders | | |
| Abnormal postoperative bleeding | 6/68 | 9% |
| Intra-articular bleeding | 0/69 | 0% |
| Minor bleeds | 36/65 | 55% |
| PT < 70% | 2/30 | 7% |
| APTT > 1,2 | 11/29 | 38% |
| Thrombopathy | 8/21 | 38% |
| Thrombopenia | 3/40 | 7% |
| Factor deficiency | | |
| V | 1/19 | 5% |
| VII | 1/19 | 5% |
| VIII | 1/19 | 5% |
| IX | 1/19 | 5% |
| X | 2/19 | 10% |
| XI | 1/19 | 5% |
| XII | 1/19 | 5% |
| von Willebrand disease | 3/20 | 15% |
| Orthopaedic involvement | | |
| Pectus carinatum and/or excavatum | 25/51 | 49% |
| Widely spaced nipples | 18/29 | 62% |
| Scoliosis | 13/66 | 20% |
| Genu valgum | 3/30 | 10% |
| Cubitus valgus | 5/30 | 17% |
| Peripheral joint pain | 12/68 | 18% |
| Diffuse pain in lower limbs | 9/68 | 13% |
| Diffuse pain in upper limbs | 0/68 | 0% |
| Axial pain | 3/68 | 4% |
| Musculoskeletal pain | 18/70 | 26% |
| Age of onset of pain | 2 - 30 | 10.9 ± 6.5 |
| Joint stiffness | 10/45 | 22% |
| Limp | 3/69 | 4% |
| Swollen joint | 1/70 | 1.4% |
| Villonodular synovitis | 1/70 | 1.4% |
| Central giant cell granuloma of jaw | 1/70 | 1.4% |
| Large joint hypermobility | 5/28 | 18% |
| Small joint hypermobility | 10/28 | 38% |
| Other anomalies | | |
| Skin hyperextensibility | 5/16 | 7% |
| SLE | 0/70 | 0% |
| Acrosyndrome | 3/68 | 4% |
| Angioma | 5/66 | 8% |

Statistics for ages are given as the minimum-maximum, average ± standard deviation. *Insufficient data. SLE: Systemic Lupus Erythaematosus, PT: Prothrombin Time, APTT: Activated Partial Thromboplastin Time, GH: Growth Hormone, SD: Standard Deviation, Minor Bleeds: easy bruising of the lower limbs, epistaxis, gingivorrhagia, menorrhagia.

Table 2: Comparison of forms with and without musculoskeletal pain with or without joint stiffness

| | Pain | | Stiffness | |
|---|--------------------|----------------------|------------------|--------------------|
| | Without | With | Without | With |
| Population | | | | |
| Boy | 33/52 (63%) | 10/18 (56%) | 22/35 (63%) | 7/10 (70%) |
| Genetic mutations | | | | |
| <i>PTPN11</i> | 37/49 (75%) | 10/16 (62%) | 22/33 (67%) | 7/8 (87%) |
| <i>SOS1</i> | 5/49 (10%) | 5/16 (31%) * | 6/33 (18%) | 1/8 (13%) |
| <i>RAF1</i> | 2/49 (6%) | 0/16 (0%) | 2/33 (6%) | 0/8 (0%) |
| <i>KRAS</i> | 3/49 (5%) | 0/16 (0%) | 2/33 (6%) | 0/8 (0%) |
| <i>BRAF</i> | 1/52 (2%) | 0/18 (0%) | 0/33 (0%) | 0/8 (0%) |
| <i>SHOC2</i> | 1/49 (2%) | 1/16 (6%) | 2/33 (6%) | 0/8 (0%) |
| Clinical characteristics | | | | |
| Compatible facial dysmorphism | 44/45 (98%) | 17/17 (100%) | 31/31 (100%) | 9/10 (90%) |
| Antimongoloid slant of palpebral fissures | 16/18 (89%) | 8/8 (100%) | 11/11 (100%) | 4/5 (80%) |
| Ptosis | 15/18 (83%) | 6/8 (75%) | 12/14 (86%) | 3/5 (60%) |
| Epicanthic folds | 7/10 (70%) | 3/3 (100%) | 4/4 (100%) | 2/3 (67%) |
| Micrognathia | 1/5 (20%) | 3/4 (75%) | 2/3 (67%) | 1/3 (33%) |
| Low-set ears | 23/24 (96%) | 9/9 (100%) | 14/14 (82%) | 3/4 (75%) |
| Short neck | 9/12 (75%) | 6/6 (100%) | 6/6 (100%) | 2/4 (50%) |
| Pulmonary stenosis | 36/52 (69%) | 9/18 (50%) | 21/35 (60%) | 5/10 (50%) |
| Size from -1.5 to -2 SD | 12/51 (23%) | 1/18 (5%) | 8/35 (23%) | 1/9 (11%) |
| Size less than -2 SD | 28/51 (55%) | 12/18 (67%) | 19/35 (54%) | 8/9 (89%) |
| Treatment with GH | 16/52 (31%) | 10/17 (59%) * | 14/35 (40%) | 5/9 (56%) |
| <i>Pectus carinatum/excavatum</i> | 17/36 (47%) | 7/14 (50%) | 11/25 (44%) | 5/8 (63%) |
| Widely spaced nipples | 14/23 (61%) | 3/5 (60%) | 7/11 (64%) | 2/4 (50%) |
| Limp | 0/52 (0%) | 3/17 (18%) * | 0/35 (0%) | 3/9 (34%) * |
| Joint stiffness | 5/30 (17%) | 5/15 (33%) | - | - |
| Joint pain | - | - | 6/10 (60%) | 4/10 (40%) |
| Diffuse pain in lower limbs | - | - | 7/33 (21%) | 1/10 (10%) |
| Swollen joint | 0/52 (0%) | 1/18 (6%) | 0/35 (0%) | 1/10 (10%) |
| Pigmented villonodular synovitis | 0/51 (0%) | 1/17 (6%) | 0/35 (0%) | 1/8 (13%) |
| Scoliosis | 10/49 (20%) | 3/17 (18%) | 2/33 (6%) | 2/10 (20%) |
| <i>Genu valgum</i> | 1/18 (5%) | 2/12 (17%) | 3/16 (19%) | 0/7 (0%) |
| <i>Cubitus valgus</i> | 3/18 (17%) | 2/12 (17%) | 2/16 (13%) | 0/7 (0%) |
| Large joint hypermobility | 3/18 (17%) | 2/10 (20%) | 3/16 (19%) | 1/7 (14%) |
| Small joint hypermobility | 7/18 (39%) | 3/10 (30%) | 7/16 (44%) | 2/7 (27%) |
| Skin hyperextensibility | 5/12 (42%) | 0/4 (0%) | 3/11 (27%) | 1/3 (33%) |
| Acrosyndrome | 2/51 (4%) | 1/17 (6%) | 3/34 (9%) | 0/9 (0%) |
| Coagulation disorder | | | | |
| Abnormal postoperative bleedings | 4/51 (8%) | 2/17 (12%) | 3/34 (9%) | 1/9 (11%) |
| Minor bleeds | 24/48 (50%) | 12/17 (71%) | 18/32 (56%) | 7/9 (78%) |
| Thrombopathy | 8/17 (47%) | 0/4 (0%) | 4/14 (29%) | 0/2 (0%) |
| Thrombocytopenia | 2/30 (7%) | 1/10 (10%) | 0/21 (0%) | 1/4 (25%) |
| PT < 70% | 1/23 (4%) | 1/7 (14%) | 1/16 (6%) | 1/3 (33%) |
| APTT > 1.2 | 8/22 (36%) | 3/7 (43%) | 4/16 (25%) | 2/3 (67%) |

***Significant result (P < 0.05)** PT: Prothrombin Time, APTT: Activated Partial Thromboplastin Time, GH: Growth Hormone, SD: Standard Deviation.

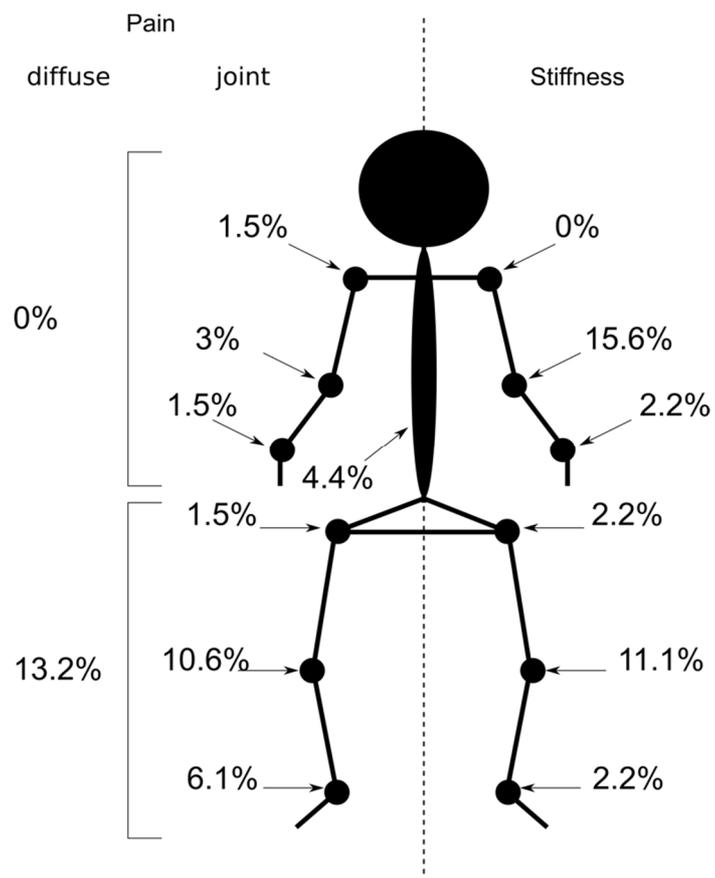


Figure 1: Location of joint involvement in patients (percentage calculated from patients with available data).