Genetic Disorders With Symptoms Mimicking Rheumatologic Diseases

Ummusen Kaya Akca
Hacettepe Universitesi Tip Fakultesi
Pelin Ozlem Simsek Kiper
Hacettepe Universitesi Tip Fakultesi
Gizem Urel Demir
Hacettepe Universitesi Tip Fakultesi
Erdal Sag
Hacettepe Universitesi Tip Fakultesi
Erdal Atalay
Hacettepe Universitesi Tip Fakultesi
Gulen Eda Utine
Hacettepe Universitesi Tip Fakultesi
Mehmet Alikasifoglu
Hacettepe Universitesi Tip Fakultesi
Koray Boduroglu
Hacettepe Universitesi Tip Fakultesi
Yelda Bilginer
Hacettepe Universitesi Tip Fakultesi
Seza Özen (sezaozen@gmail.com)
Hacettepe University https://orcid.org/0000-0003-2883-7868

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Abstract

Background

Musculoskeletal symptoms may be due to non-inflammatory causes including genetic disorders. We aimed to examine the final genetic diagnosis in patients who had presented with musculoskeletal complaints to rheumatology department.

Methods

Patients presenting to the department of pediatric rheumatology and consulted to the genetic department between January 2015 and May 2019 were evaluated retrospectively.

Results

A total of 60 patients, 19 boys (31.66%), with a mean age 12.46 ± 1.41 years were included in the study. Total consanguinity rate was 25%. The most common (29.5%) cause of referral to the genetic department was the presence of skeletal anomalies (such as camptodactyly, clinodactyly, and short stature) with accompanying joint findings. Approximately one third of the patients (n: 19) were diagnosed and followed up by the genetic department. The diagnoses of patients were as follows; CACP syndrome (n:3), trichorhinophalangeal syndrome (n:1), progressive pseudoromatoid dysplasia (n:2), LIG4 syndrome (n:1), H syndrome (n:1), SPENCD syndrome (n:3), and nonspecific connective tissue disease (n:8).

Conclusions

In the differential diagnosis of patients who are referred to the department of pediatric rheumatology with complaints of the musculoskeletal system, genetic disorders should also be taken into consideration.

Clinical Trial Registration: Hacettepe University Ethics Commission (Approval number: GO 19/781)

Background

Musculoskeletal complaints may be the initial presenting symptoms in a number of genetic diseases (1). Musculoskeletal system symptoms may occur as part of genetic syndromes or genetic skeletal disorders that affect the development and growth of cartilage or bone. Patients with genetic skeletal disorders may present with disproportionate short stature, scoliosis, extremity anomalies (such as curvature in long tubular bones, brachydactyly, camptodactyly, limb asymmetry) or recurrent joint dislocation (2). Progressive pseudo rheumatoid dysplasia (PPRD) and CACP syndrome (camptodactyly, arthropathy, coxa vara deformity and pericarditis) can mimic juvenile idiopathic arthritis (3, 4). Correct diagnosis is often delayed in these patients (5). The absence of signs of inflammation (morning stiffness, redness, tenderness) and normal (laboratory) inflammatory markers may suggest non-rheumatologic diseases (6). A detailed history of symptoms, family history, a pedigree of at least three generations, a systemic examination including anthropometric measurements, laboratory tests and radiologic examination are required to identify such genetic disorders (7). Accurate diagnosis of genetic disorders also helps in predicting the natural course and prognosis of the disease, providing proper genetic counseling and avoidance of unnecessary treatment.

We aimed to present our single center experience with genetic disorders mimicking rheumatic diseases with similar symptoms. We hope these cases will raise awareness for these genetic disorders, in the differential for our common diseases.

Methods

This study includes retrospective analysis of 60 patients who were admitted to our department of pediatric rheumatology with musculoskeletal complaints considered not to be associated with rheumatic diseases between January 2015 and December 2019; these patients were consulted to genetics department. Patients who were evaluated and diagnosed by another genetic center were not included in the study. The rate and degree of consanguinity, clinical diagnosis, indication for consultation, accompanying musculoskeletal and other findings were all recorded. Anthropometric measurements (height and weight) were obtained using percentile values of Turkish children (8). Short stature was defined as the height that is 2 standard deviations (SD) or more below the mean for children of that sex and chronologic age. The diagnosis of genetic disorders were primarily based on a detailed history including family history, pregnancy history, neonatal history, developmental milestones and current schooling provision, physical examination including dysmorphology examination and assessment of behavioural phenotype, radiological evaluations when necessary and genetic analysis. "Definite clinical and molecular diagnosis" were established by means of history, physical examination, radiologic assessments and genetic analysis whenever available. Patients in whom no genetic etiology could be revealed but the diagnosis was made on clinical and radiological grounds were defined as "definite clinical diagnosis", and patients diagnosed with only clinical findings were defined as "strongly probable diagnosis" (9).

Ethical approval for this study was obtained (Project No: GO 19/781). Written informed consent was given from patients or their parents for publication of genetic analysis results. Statistical analyses were performed by using the SPSS version 20 package. Descriptive statistics were presented as frequency, percentage, mean, SD and median values.

Results

A total of 60 patients, 19 boys (31.6%), with a mean age of 12.46 ± 1.41 years were included in the study. The rate of consanguinity was 25.0%. Parental first cousin marriage and $\geq$ 2nd cousin marriages were detected in 10 (16.6%) and 5 (8.3%) families, respectively. The reasons for admission to the rheumatology follows; joint swelling (n = 15/60, 25.0%), extremity deformity (n = 12/60, 20.0%), arthralgia (n = 11/60, 18.3%),

skin rash (n = 9/60, 15.0%), abdominal pain and fever (n = 4/60, 6.6%), Raynaud syndrome (n = 3/60, 5.0%) and other reasons (oral aphthous ulcers, edema, dry mouth and dry eye) in 6 (10.0%) patients.

The most frequent (n = 12/60, 20%) reason for referral to the genetic department was the presence of skeletal anomalies such as camptodactyly, clinodactyly, and shortness in tubular bones accompanying joint findings. Other causes in decreasing frequency were as follows; accompanying findings such as neurocutaneous findings and family history that are suggestive of a genetic syndrome (n = 11/60, 18.3%), joint hyperlaxity (n = 10/60, 16.6%), dysmorphic facial features (n = 9/60, 15%), joint deformity (n = 5/60, 8.3%), other joint findings without clinical and laboratory signs of inflammation (n = 5/60, 8.3%), short stature (n = 4/60, 6.6%), and abnormal radiological findings suggestive of a genetic disorder (n = 4/60, 6.6%).

The most commonly affected joints in all patients, in general, were hands, knees and spine (Fig. 1) whereas in 19 patients with a genetic disorder, the most commonly affected joints were hands, knees, and hips.

In the laboratory evaluation of patients presenting with joint swelling and arthralgia, acute phase reactants including erythrocyte sedimentation rate and C-reactive protein concentrations were all within normal laboratory reference values.

Among these 60 patients, 19 (n = 19/60, 31.6%) had a final diagnosis of a genetic disorder. The diagnoses in decreasing frequency were as follows; nonspecific connective tissue disease (n:8), CACP syndrome (n:3), SPENCD (n:3), progressive pseudoromatoid dysplasia (n:2), trichorhinophalangeal syndrome (n:1), LIG4 syndrome (n:1), and H syndrome (n:1). Parental consanguinity was present in 25% of patients. The rate was similar among patients with a genetic disorder (25.0% vs 25.0%). Among the patients with genetic diagnosis (n = 19), six patients (31.5%) had a definite clinical and molecular diagnosis while five patients (26.3%) had definite clinical diagnosis. Clinical features of patients with definitive clinical and molecular diagnosis and definite clinical diagnosis are shown in Table 1.

Table 1
Clinicinal, radiological and moleculer features of patients with "definite clinical and molecular diagnosis" and "definite molecular diagno

Patient no	Gender	Age at diagnosis	History of consanguinity of families (Degree of consanguinity)	Reason for application to rheumatology department	Consultation indication	Physical examination findings	Radiologic specific findings	Diagnosis grouping	M di
1	Girl	5	Yes (1st degree cousin marriages)	Swelling of joints	Camptodactyly, arthritis	Restriction in the right elbow and both wrists, swelling in both hands and knee joints, camptodactyly in 2nd and 3rd fingers of both hands, limited abduction of the right hip	Camptodactyly in the hands	Definite clinical and molecular diagnosis	H *P* m
2	Girl	12	No (originated from same village)	Swelling of joints	Camptodactyly, clinodactyly, arthritis	Extension limitation in bilateral elbow joints, camptodactyly in the thumbs of both hands, joint swelling in the elbows, knees, and left hip restriction	Camptodactyly in the hands,	Definite clinical and molecular diagnosis	H *P* m
3	Boy	9	No	Swelling of joints	Curvature and joint swelling in the fingers, taken treatment as a JIA patient but did not benefit from it	Extension restriction in the joints of the hand, camptodactyly in 3rd, 4th and 5th fingers of right hand	Camptodactyly in the hands	Definite molecular diagnosis	N m
4	Girl	12	No	Curvature of her fingers	Camptodactyly and facial findings	Clinodactyly in 2nd, 3rd, 4th fingers of right hand and middle finger of the left hand. Short structure, prominent nose tip, thin upper lip, and sparse hair.	On hand MRI imaging, epiphyseal irregularities in the PIF joint faces of middle phalanges, deformities, and shortness of the 4th and 5th metacarpes of the right hand	Definite molecular diagnosis	N in Fl ar
5	Girl	12	No	Swelling of joints for two years	Polyarticular involvement without arthralgia and normal acute phase reactants response	Swelling and enlargement in proximal interphalangeal joints of 2-5th fingers on right hand	Epiphyseal enlargement of the metacarpophalangeal and interphalangeal joints	Definite molecular diagnosis	N m
6	Boy	16	Yes (1st degree cousin marriages)	Hip and low back pain	Compatible findings with PPRD in thoracolumbar MRI	Low back pain and swelling of knee and elbow joints	In radiological examination of the spine, platyspondyly of vertebral bodies, anterior wedging of vertebrae, and erosion in the end plates. Enlarged epiphyses of the femoral heads.	Definite molecular diagnosis	N m
7	Boy	19	Yes (2nd degree cousin marriages)	Joint swelling, oral and genital aphthae	Accompanying diseases (hypothyroidism, growth hormone deficiency, recurrent meningitis and respiratory problems, and developmental delay)	Short stature, normal joint examination	-	Definite clinical and molecular diagnosis	*L* m
8	Girl	14	Yes (1st degree cousin marriages)	Limited joint range of motion	Accompanying diseases (hyperpigmented lesions, diagnosis of tip1 diabetes mellitus, short stature and signs of hypogonadism)	Short stature, purple-black colored hyperpigmented lesions which were more prominent on the legs, contracture in the proximal in interphalangeal joints of bilateral hands	-	Definite clinical and molecular diagnosis	H de ex S

Patient no	Gender	Age at diagnosis	History of consanguinity of families (Degree of consanguinity)	Reason for application to rheumatology department	Consultation indication	Physical examination findings	Radiologic specific findings	Diagnosis grouping	M di
9	Boy	6	No	Arthralgia and arthritis	Physical examination and radiologic findings	Short stature, arthritis of right first metacarpophalangeal joint, and arthralgia of left knee, both ankles, elbows, and neck	Platyspondyly with irregular vertebral endplates, flattening of the posterior vertebral bodies, metaphyseal changes in the long bones, enchondromatous lesions in distal radius and ulna, and dense calcifications in the basal ganglia	Definite clinical and molecular diagnosis	H *A* m
10	Girl	16	No	Arthralgia and arthritis	Physical examination and radiologic findings	Short stature, arthralgia, and arthritis of bilateral metacarpophalangeal joints	Metaphyseal changes in the long bones, platyspondyly in the vertebral bodies, and dense intracranial calcifications	Definite clinical and molecular diagnosis	H *A* m
11	Girl	16	Yes (1st degree cousin marriages)	Malar rash, fever, rash and arthralgia	Physical examination and radiologic findings	Malar rash, arthralgia, and short stature.	Platyspondyly in vertebra and metaphyseal changes	Definite molecular diagnosis	N

Eight patients are still under follow up in the genetic department with the strongly probable diagnosis of "Nonspecific connective tissue disorder". These patients were questioned in terms of hereditary connective tissue diseases (HCTD) because of the detection of the finding of joint hypermobility on physical examination. Accompanying clinical findings included easy bruising (n:3), pes planus (n:2), a history of spontaneous pneumothorax (n:1), cardiac defect (n:1) and striae (n:1).

Direct radiography findings contributed to the diagnosis especially in six patients. Epiphyseal enlargement of the metacarpophalangeal and interphalangeal joints (patient 5), and enlarged epiphyses of the femoral heads, platyspondyly of vertebral bodies, anterior wedging of vertebrae, and erosion in the end plates (patients 6) were observed in patients with PPRD (Fig. 2). Radiologic examination of patient 4 revealed cone-shaped epiphyses that were highly suspicious for tricho-rhino-phalangeal syndrome (TRPS) (Fig. 3). In addition, in the radiological examination of the 9th, 10th and 11th patients, platyspondyly with irregular vertebral endplates, flattening of the posterior vertebral bodies, metaphyseal changes in the long bones, and enchondromatous lesions in distal radius and ulna were consistent with radiographic findings of SPENCD (Fig. 4).

Discussion

In this study a total of 60 patients who were initially admitted to the department of pediatric rheumatology but were thought to have associated genetic diseases were evaluated retrospectively. One third of patients (n = 19/60, 31.6%) who were subsequently evaluated at the genetic department, were diagnosed with a genetic disorder. Considering that the diagnosis rate is very high, the threshold value should be kept low in terms of genetic diseases.

Non-rheumatic diseases are a substantial part of the pediatric rheumatology department referrals. As a result of a 3-year study conducted by the Pediatric Rheumatology Database Research Group in the United States, 12,939 patients recorded in the registry and over 50% of the patients had non-rheumatic diagnosis (10). Similarly, among 3269 patients who applied to the pediatric rheumatology department between 1981 and 2004, a diagnosis was established in 2026 patients (61.9%): The diagnosis were rheumatic diseases in 1032 (50.9%) and non-rheumatic disease in 994 (49.1%) of the patients (11). Distribution of nonrheumatic disease were orthopedic, mechanical or traumatic condition (n:345), infection (n:231), hematologic or neoplastic disease (n:45) and variety of other conditions (n:336). Genetic disease was present in 14 of 336 patients in the category of other conditions and most frequent of them (n:4) were HCTD. In our study, a total of 30432 patients applied to the pediatric rheumatology department over a period of 5 years. and among them, 60 were consulted to the genetic department. Of these 60 patients, a diagnosis of a genetic disorder could be established in 19 (31.6%) of them. Hereditary connective tissue disorders represented the most common (n = 8/19, 42.1%) diagnosis in our group.

Joint swelling, deformity in the extremity, arthralgia, and skin rash were the most of the symptoms for applying to the rheumatology department of consulted patients. We referred the patients to the genetic department due to the presence of skeletal anomalies, short stature, joint deformity, joint hyperlaxity, and dysmorphic findings, multiple anomalies, genetic diagnosis suspicion according to the results of radiological examination, and the lack of clinical and laboratory signs of inflammation. They has some common features of skeletal dysplasias such as short stature, ligamentous laxity, spinal deformity, progressive finger contractures, and extremity deformities (12, 13). Systemic physical examination, systemic findings, evaluation of growth and development, family history and concomitant diseases give an idea in terms of possible genetic disorders (14).

Radiologic examination has a crucial role in the diagnosis of rheumatologic diseases. Radiological imaging methods provide noninvasive information about the pathological processes developing in the musculoskeletal system, and helps the diagnosis. Six patients with definitive clinical diagnosis had direct radiography findings specific to the diagnosis in our study. Direct radiography which is the basic method of imaging provide a differential diagnosis as well as

diagnosis of rheumatological diseases (15). According to European League against Rheumatism (EULAR)—Pediatric Rheumatology European Society (PReS) recommendations, direct radiography is recommended especially for the detection of structural abnormalities (16).

Genetic skeletal disorders can mimic juvenile idiopathic arthritis. Camptodactyly-arthropathy-coxa vara-pericarditis (CACP) syndrome (OMIM 208250) is a rare autosomal recessive disease characterised with early-onset camptodactyly, noninflammatory arthropathy, progressive coxa vara deformity and noninflammatory pericardial effusion. CACP is caused by homozygous mutation in the *PRG4* gene (OMIM 604283) on chromosome 1q31 (17). PRG4 encodes the protein lubricin which is involved in the diffusive behavior of synovial fluid and contributes to the elastic absorption and energy dissipation of synovial fluid at physiologic shear frequencies (18). Joint findings of CACP syndrome may be confused with the joint findings of juvenile idiopathic arthritis (7). Many mutations have been identified in the PRG4 gene and new mutations continue to be identified (19). Diagnosis of CACP is based on clinical findings, radiologic and echocardiography findings. Genetic testing can confirm the diagnosis. However, the absence of a mutation does not exclude the diagnosis.

Another genetic skeletal disorder which may be confused with juvenile idiopathic arthritis is progressive pseudorheumatoid dysplasia (PPRD, OMIM 208230) which is an autosomal-recessive disease caused by mutations in the WISP3 (Wnt1-inducible signaling pathway protein 3, OMIM 603400) gene. Patients usually present with polyarticular involvement and gait abnormalities. Subsequently, involvement of the large joints and spine can accordingly cause severe joint contractures, hip disease and spinal deformities (20, 21). Swelling in the interfalengeal joints may be confused with polyarticular juvenile idiopathic arthritis, however inflammatory markers are normal and they do not respond to antirheumatic therapy (22). Numerous WISP3 mutations have been reported. However intronic mutations leading to splicing aberrations can only be extracted from cultured skin fibroblasts. As in our two cases, the absence of mutation in the WISP-3 gene does not rule out the diagnosis of PPRD without making cultured skin fibroblasts.

Tricho-Rhino-Phalangeal syndrome tip 1 (TRPS, OMIM 190350) is characterized craniofacial and skeletal abnormalities. The main findings are sparse, thin hair, bulbous nasal tip, short stature, cone-shaped epiphyses of the hands and feet which were present in our patient (23). Diagnosis of TRPS is frequently based on clinical and radiological findings since the phenotype is often evident (24). We reported a case with clinical and radiological features (especially cone-shaped epiphyses) that were highly suspicious for TRPS. A confirmatory genetic diagnosis was not available since we could not perform DNA sequence analysis.

Spondyloenchondrodysplasia (SPENCD, OMIM 607944) is a rare autosomal recessive skeletal dysplasia which is characterized with neurological involvement and immune dysfunction (25). SPENCD is an interferonopathy. SPENCD patients should be monitored for SLE and other comorbidities, while the possibility of SPENCD should be considered in SLE patients with short stature and skeletal abnormalities. Metaphyseal changes in the long bones and platyspondyly in the vertebral bodies are radiographic findings of SPENCD as seen all three of our patients as we reported before (26).

This study has some limitations. This study is for a selected group of patients who were initially referred to the department of pediatric rheumatology. Patients who were initially referred to the department of genetics who were not included in the study. Larger-scale and multi-center studies are needed. Despite this limitation, to our knowlegde, this study yet represents the first kind of its own evaluating the diagnostic profile of consulted patients in the literature.

Conclusion

In conclusion, in patients who apply to rheumatology outpatient clinics with musculoskeletal findings without inflammation, concomitant diseases should be considered. Summarizing the genetic diagnostic spectrum detected in these patients will hopefully increase the awareness of the physicians involved in patient care.

Abbreviations

CACP syndrome
Camptodactyly, arthropathy, coxa vara deformity and pericarditis syndrome
EULAR
European League against Rheumatism
HCTD
Hereditary connective tissue diseases
PPRD
Progressive pseudo rheumatoid dysplasia
PReS
Pediatric Rheumatology European Society
SPENCD
Spondyloenchondrodysplasia
TRPS
Tricho-rhino-phalangeal syndrome

Declarations

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Conflict of Interest: The other authors have indicated they have no potential conflicts of interest to disclose

Clinical Trial Registration: Hacettepe University Ethics Commission (Approval number: GO 19/781)

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Authors' contributions

UKA conceptualized and designed the study, drafted the initial manuscript, reviewed and revised the manuscript. POSK contributed to the data collection, study design and as well as approved the final manuscript as submitted. GUD conceptualized and designed the study, and approved the final manuscript as submitted. ES drafted the initial manuscript and conceptualized the study. EA designed the study and drafted the initial manuscript. GEU contributed to the data collection and drafted the initial manuscript. MA contributed to the data collection and approved the final manuscript as submitted. KB coordinated and supervised data collection, approved the final manuscript as submitted. YB designed the study, critically reviewed and revised the manuscript. SO coordinated and supervised data collection, and critically reviewed and revised the manuscript.

Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Consent for publication

All authors give consent for publication.

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Figures

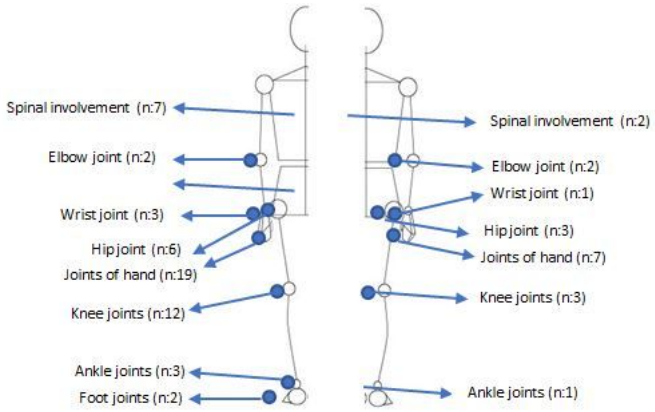

Figure 1

Distrubition of joint involvement (in all consulted patients on the left, in diagnosed with genetic disease on the right)

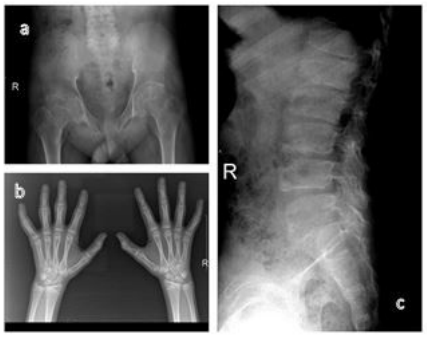

Figure 2

Radiological images of patients with PPRD (a: enlarged epiphyses of the femoral heads, b: epiphyseal enlargement of the metacarpophalangeal and interphalangeal joints, c: platyspondyly of vertebral bodies, anterior wedging of vertebrae, and erosion in the end plates)

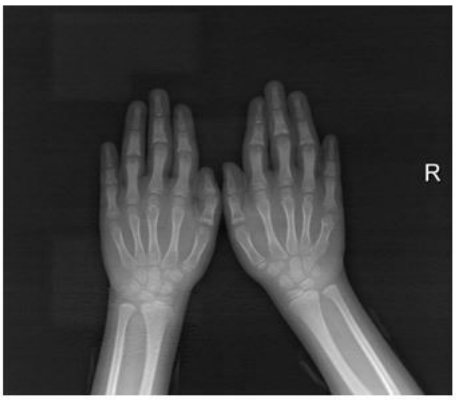

Figure 3

Patient 3: X-ray of the hands showing cone-shaped epiphyses of the 2nd to 4th middle phalanges

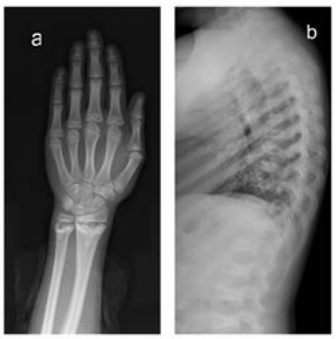

Figure 4

Radiological images of patients with SPENCD (a: metaphyseal changes in the long bones, b: platyspondyly with irregular vertebral endplates, flattening of the posterior vertebral bodies)