RHEUMATIC DISEASES AND KLINEFELTER’S SYNDROME.
REVIEW

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Abstract

The article summarises reports on the concurrence of Klinefelter’s syndrome with inflammatory rheumatic diseases, rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, polymyositis/dermatomyositis, systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, the antiphospholipid syndrome, and ankylosing spondylitis. These include two case reports of patients with Klinefelter’s syndrome concurrently associated with rheumatoid arthritis or antisynthetase syndrome respectively, previously reported by the author and his co-workers. Attention is paid to the pathogenesis and the course of the disease in patients with Klinefelter’s syndrome. The importance of early diagnosis of the syndrome, when occurring simultaneously with other diseases of connective tissue, is emphasised.

Keywords

Klinefelter’s syndrome, Rheumatoid arthritis, Juvenile idiopathic arthritis, Psoriatic arthritis, Polymyositis/dermatomyositis, Systemic lupus erythematosus, Systemic sclerosis, Mixed connective tissue disease, Antiphospholipid syndrome, Ankylosing spondylitis

Abbreviations used

KS, Klinefelter’s syndrome; RA, Rheumatoid Arthritis; JIA, Juvenile Idiopathic Arthritis; LH, Luteinising Hormone; SLE, Systemic Lupus Erythematosus; ANA, Antinuclear Antibodies; BWR, Bordet-Wasserman Reaction; MTX, Methotrexate; PsA, Psoriatic Arthritis; PM, Polymyositis; DM, Dermatomyositis; SSC, Systemic Sclerosis; MCTD, Mixed Connective Tissue Disease; APS, Antiphospholipid Syndrome; AS, Ankylosing Spondylitis

Introduction

Klinefelter’s syndrome (KS) is not a rare gonosomal aberration occurring in males. The disorder is characterised by micro-orchidism. Another typical, although not constant, symptom of this disorder is gynecomastia with almost normal male secondary sex characteristics. The aetiology of the disease remains unexplained. Previous studies have shown that this disorder is a genetic chromosomal abnormality associated with the presence of one additional chromosome due to abnormal division. Thus, the affected individual has 47 chromosomes with the resulting chromosomal constellation of XXY (classical form) or 46,XY/47,XXX (mosaic form).
In large population studies the incidence of KS has been estimated to be 1:1000 liveborn male babies (1). The locomotor apparatus of persons affected by the syndrome is characterised by acromicria, clinodactyly, concrescence of thoracal vertebral bodies, and spinal osteoporosis is found not only in individuals of older age but also in younger persons.

In 1960s and 1970s, reports have been published on the concurrence of KS with autoimmune diseases. The aim of the present article is to discuss KS case reports published by the author and his co-workers as well as to present an overview of the reports published so far, mainly abroad.

RESULTS

KLINEFELTER’S SYNDROME AND RHEUMATOID ARTHRITIS (RA)

Bošmanský and Kopecky (2) described the development of RA in a 61-year-old patient with KS; the patient was diagnosed with RA at the age of 55.

RA had a clearly benign development, slow progression, and mild aggressiveness and minimal exudative manifestations may be attributed to the presence of KS and concurrently developed diabetes mellitus. ESR values were moderately elevated. Rheumatoid factors gave positive results (LFT 1280, HT 112). ELFO: elevated alpha2 and gamma globulins. Diffuse ischaemic changes could be identified on the ECG. The patient died after suffering a myocardial infarction.

In their report, Bošmanský and Kopecky (2) pointed to the relatively rare coincidence of KS and RA. The cases reported in the available pre-1979 literature included a case of RA, type II insulin resistant diabetes mellitus, and KS in a 41-year-old patient (3); Mac Sween’s (4) reported on a patient with malignant lymphoma, RA, and KS; the description by Tsung et al. (5) of a 46-year-old patient with KS and the presence of high titres of rheumatoid factors, malignant lymphoma, and Osler-Weber-Rendu’s syndrome. Kobayashi et al. (6) also described a patient with KS associated with RA.

Both RA and KS are diseases in which perturbations of the gonadal axis has been reported. Low testosterone levels or increased estradiol:testosterone ratio have been considered as a contributing factor in the development of RA in males (7, 8). In RA males estradiol was found to be correlated with the degree of inflammation (9). In addition to this, the local action of gonadal steroids, determined by factors such as conversion to active metabolites or receptor sensitivity in tissues affected with inflammation, may also play an important role in RA pathogenesis (10). Although the underlying mechanism of the gonadal axis perturbations in RA is likely different from that in KS, the hypoandrogenic status found in both diseases on a systemic level might explain the concurrence of KS with autoimmune disorders. Furthermore, genetic abnormalities in androgen receptor coding genes such as polyglutamine repeat length were found to contribute to phenotypic variability in KS suggesting alterations in androgen action and may indeed play a role in the development of
autoimmunity in KS as well (11). On the other hand, Kobayashi et al. (6) are inclined to believe that low testosterone levels need not represent a predisposition factor for RA activity. The course of the disease in their patient was benign, similarly as in the case report by Bošmanský and Kopecký (2).

Klinefelter’s Syndrome and Juvenile Idiopathic Arthritis (JIA)

Mirkinson et al. (12) published a case of KS and JIA. The patient, a 16-year-old Caucasian male, was referred for evaluation of a 3-year history of bilateral “claw hand” and diffuse morning stiffness of the proximal and distal phalanges of both hands. At the time of his initial visit, his morning stiffness lasted for 60 min. He denied symptoms of pain or swelling of other joints or the back, with the exception of decreased lateral flexion of his neck.

The patient was diagnosed with KS with a 47 XXY karyotype at the age of six. Evaluation was prompted by concerns of developmental delay and attention deficit disorder. Consistent with this diagnosis, transdermal testosterone therapy was started at age 14. At the time that supplemental testosterone therapy was begun, the patient’s testosterone level was 0.1 ng/dl (normal 3.0–10.0 ng/dl) and the luteinising hormone (LH) was < 0.09 mIU/ml (normal 2.4–9.4 mIU/ml). At the time of his initial evaluation for arthritis, his only medication was a testosterone patch applied daily.

At the time of his initial evaluation, a diagnosis of polyarticular JIA was made. The patient was initially started on non-steroidal anti-inflammatory drugs (NSAID) therapy. Three months later, oral methotrexate (MTX) at a dose of 10 mg weekly (0.18 mg/kg/week) was added to his regimen due to continued evidence of active inflammation manifested by joint swelling and morning stiffness. A marked improvement in morning stiffness and joint swelling was noted when the MTX therapy was increased to a dose of 0.3 mg/kg/week. A resolution of clinical signs of active inflammation was achieved 9 months after the initiation of MTX. NSAID therapy was later discontinued and the patient was treated with a maintenance dose of 0.2 mg MTX/kg/week.

The development of autoimmune disease, in this case JIA, in patients with KS may be indicative of the relationship between autoimmunity and androgen/oestrogen balance. Whether or not KS predisposes to autoimmune disease because of its associated decreases in androgens or if these hormonal decreases are the result of disease is not yet clear.

Klinefelter’s Syndrome and Psoriatic Arthritis (PsA)

Melillo et al. (13) reported on a case of KS and PsA. This case report emphasises the role played by sex hormones and chromosomal abnormalities in the pathogenesis of autoimmune disorder, and to our knowledge, this is an uncommon case of a patient with KS who developed PsA.
Klinefelter’s Syndrome, Polymyositis (PM) / Dermatomyositis (DM)

Rovenský et al. (14) reported on a case of a patient with KS associated with the antisynthetase syndrome (Raynaud’s phenomenon, acrosclerosis, mechanic’s hands, mild weakness of proximal muscles of the hands, presence of interstitial pulmonary fibrosis, tendency to recurrent infections, and secondary Sjögren’s syndrome). The presence of anti-Jo-1 antibody together with anti-Ro and anti-La antibodies was detected upon repeated tests. Two cases of a similar association have been reported from South Africa by Nielsen et al. (15) and Murakami et al. (16). The latter cases concerned concurrence of classical polymyositis with KS.

Klinefelter’s Syndrome and Systemic Lupus Erythematosus (SLE)

Among other rheumatic diseases, several cases of SLE have been reported. Ortiz-Neu and LeRoy (17) reported the coincidence in 1969. The authors presented two patients with KS and SLE. Their third patient with KS had a finding of glomerulonephritis with antinuclear antibody positivity. Later on, Vittori and Desaegher (18) referred to other papers such as those by Landwirth and Berger (19), and Saeed Uz Zafer et al. (20). The latter group even described a case of KS, SLE, and porphyria cutanea tarda. Folomeev et al. in 1991 (21) described the case of a 22-year-old male in whom SLE appeared to be characterised by Raynaud’s phenomenon with necrosis of the fingers, dyspnoea, and chest pain due to pleuritis. Among the laboratory parameters, the presence of antinuclear antibodies (ANA) was detected, and the Bordet-Wasserman reaction (BWR) gave false positive results. Some 10 years later, the patient was again admitted for skin rash, sensitivity to sunrays, and ulcers in the oral cavity. Moreover, Raynaud’s phenomenon was presented, with necroses of fingertips and lymphadenopathy. The laboratory parameters showed leucopenia, high ESR values, and LE cell positivity, elevated ANA titres, presence of anti-ds DNA antibodies, anticardiolipin antibodies and lupus anticoagulants, mild proteinuria, and pulmonary infiltrates were detected. The patient’s androgen plasma levels were decreased and his oestrogen levels were elevated. KS was unambiguously proved by endocrinological and genetic tests.

Stern et al. (22) studied urinary oestrogen levels in KS and SLE. One patient had elevated levels of all the three urine oestrogens studied (estrone, estradiol and estriol), with the estriol levels being markedly elevated. No such findings could be identified in another patient who, however, had an altered oestrogen metabolism detected by labelled estradiol, i.e. disturbed estradiol to estrone conversion. Subsequent conversion to estriol was enhanced in both patients. These results suggested excessive estradiol transformation into estriol and a reduced metabolism of 2-OH estrone. Lahita (23) pointed to the fact that estradiol levels are frequently elevated in KS, reaching values as measured in women with the normal menstrual cycle, whereas androgen levels are similar to those found in prepubertal age males. Oestrogens seem to play a role in the modulation of the immune system and a significant role in the pathogenesis of SLE itself. Other studies showed that plasma androgen levels,
including those of testosterone, androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone sulphate are reduced in SLE. Michalski et al. (24) described a patient with testicular insufficiency, reduced testosterone and increased follicle stimulating and luteinising hormone levels as may be expected in patients with KS. Lahita and Bradlow (25) studied several patients with KS and SLE and concluded that their metabolism of sex steroids was similar to that observed in women suffering from SLE. French and Hughes (26) pointed also to testicular insufficiency in patients with SLE. The above-mentioned cases however failed to clarify whether it is hyperoestrogenism or a lack of testosterone or both that are responsible for the development of autoimmunity in these individuals. Androgens seem to be natural immunosuppressors, and their deficiency was observed in SLE and in RA males.

The list of reports on patients with SLE and KS concludes with a paper by Gilliland and Stashower (27,) who described a case of a 12-year-old boy in whom epileptic episodes were occurring since he was 4 years old. Initially, he experienced skin manifestations on his face and shoulders as well as in the auricular region. Biopsy suggested discoid lupus erythematosus. Weakness and arthritis of small joints of the hands and feet developed after several months. ANA, anti-dsDNA antibodies, hypocomplementaemia, mild lymphopenia, and elevated ESR values were present. The disease could be controlled by antimalarials and prednisone. Upon a follow-up examination at the age of 16 years the patient was found to have small testes. Hormone and chromosome analysis confirmed the presence of KS. The patient was subsequently treated with 200 mg testosterone at 3-week intervals. The skin symptoms worsened at the age of 19 years, accompanied by hair loss and arthritis, the only laboratory parameter positivity being ANA.

It is known from epidemiological surveys in our region that for SLE, the females-to-males ratio is 9:1. The incidence of KS has been estimated at 1.7 / 1000 males born and the simultaneous occurrence of both syndromes may actually be coincident. On the other hand, there have been attempts at screening male patients with SLE for the presence of KS. Dubois and Kaplan (28) attempted to disclose the presence of KS in 22 male patients with SLE using swaps from buccal mucosa. No KS could be identified. Upon physical examination of young males with diagnosed SLE it is important to seek for hypogonadism and gynecomastia, and to pay attention to secondary sexual characteristics.

There have been but two studies published so far that focused on the effects of testosterone therapy on clinical manifestations in SLE patients. Bizzarro et al. (29) pointed to the fact that testosterone administration in two patients with SLE was followed by clinical and immunological remission in both of them. In their patient, Olsen and Kovacs (30) administered testosterone replacement therapy and brought his testosterone levels to normal. These authors described both a clinical improvement and an improvement of haematological and serological parameters during a 9-month therapy. A similar clinical and laboratory improvement was observed during testosterone replacement therapy in males suffering from RA (31).
The paper by Strand (32) suggested that dehydroepiandrosterone replacement is possible for SLE. It is mainly used in the treatment of corticosteroid dose-dependent SLE, it improves bone density and the lipid spectrum. In other words, progress in hormonal therapy of SLE is suggested in this direction and it cannot be ruled out that this method of treatment will also be used for other autoimmune diseases or to treat concurrent KS and SLE, and/or other nosological entities.

**Klinefelter’s Syndrome and Systemic Sclerosis (SSc)**

Nowlin et al. in 1985 (33) described the occurrence of KS with SSc. A short description was published earlier by O'Donoghue (34). In one of the two patients described by Nowlin, hypogonadism had been present prior to the development of SSc. The authors discussed the role of testicular failure as a disease-modifying factor in SSc. In the other patient, Raynaud’s phenomenon appeared with a lack of androgens. Testicular fibrosis along with vasculopathy are believed to contribute to gonadal failure in SSc. DeKeyser et al. (35) reported on a case of SSc with KS with the clinical picture being dominated by sclerodactyly and bilateral basilar pulmonary fibrosis, synovitis of the MCP joints. Again, the authors speculated about the potential effects of the KS on the development of the autoimmune syndromes. This mainly concerns the effects of the doubling of the X chromosome and the low androgen-to-oestrogen ratio. And finally, Kobayashi et al. (36) described SSc in a patient with KS, who had been infertile for 20 years of marriage; SSc and KS was diagnosed at the age of 43 years. The authors mentioned a total of 5 cases of SSc in persons of 41–61 years of age, and speculated about the association between KS and SSc.

**Klinefelter’s Syndrome and Mixed Connective Tissue Disease (MCTD)**

Takeuchi et al. (37) published a report of a patient with KS presenting with MCTD, diabetes mellitus, and some other endocrine disturbances. Upon admission, the 57-year-old male showed polyarthritis, sausage fingers, and Raynaud’s phenomenon in his clinical picture. Restrictive disturbance of the diffuse pulmonary capacity, and a myogenic lesion were demonstrated upon EMG, along with anti-RNP antibody positivity and diabetes mellitus, hyperprolactinaemia, hypothyreosis, and hypocorticism.

Kasten et al. (38) described a 43-year-old male with eunuchoid body proportions and a history of deep venous thromboses in the right leg presented with recurrent ulcers in the right perimalleolar region for 6 years. Karyotyping revealed a 47 XXY KS, while serological testing showed protein S deficiency, hyperhomocysteinaemia, and a positive lupus anticoagulant. He also had mixed connective tissue disease (Sharp’s syndrome) with acrosclerosis, proximal finger oedema, Raynaud’s phenomenon, and high titres of ANA and U1–RNP-antibodies, as well as osteoporosis. There is evidence that patients with KS are prone to develop connective tissue diseases and thrombophilia as a result of low androgen levels.
Klinefelter’s Syndrome and Antiphospholipid Syndrome (APS)

Miyagawa et al. (39) described the occurrence of KS in a patient with SLE, presenting with ulcerous formations on lower extremities. The patient was found to produce anticardiolipin antibodies that may play a role in the development of occlusive alterations in peripheral arteries. The association of the antiphospholipid syndrome with KS was first described in 1993. Later on, two cases of SLE with a secondary antiphospholipid syndrome in KS were reported by Folomeev (21) and Bajocchi et al. (40). Miyagawa et al. (39) pointed to the fact that the immune mechanism including the beta 2-GPI cofactor may contribute to the reasons underlying vascular alterations in KS.

Klinefelter’s Syndrome and Ankylosing Spondylitis (AS)

Armstrong et al. (41) described the presence of KS together with AS. They suggested that the development of AS in their patient was clinically substantially milder than the course of the disease in the patient’s father. Upon the clinical examination of the patient, severely limited movements of the neck and limited movements of the chest upon expiration and inspiration were observed, bilateral sacroilitis, and fusion of cervical and apophyseal joints. On the other hand, lumbar spine showed only relatively mild alterations and demarcated calcifications within interspinal ligaments, and sclerosis of the annulus fibrosus apposition. Early quadratisation of lumbar vertebrae was observed. In the patient’s father, movements of the shoulder joints were limited and painful, along with a pronounced restriction of movements in all spinal segments, fusion of sacroiliac joints, quadratisation, and bony bridges between the vertebral bodies within the lumbar segment of the spine. No fusion of apophyseal joints was seen. The cervical spine suggested cervical spondylosis. The course of the disease in the patient seemed to be similar to the course of the disease in females: previous authors, e.g. Resnick et al. (42), suggested that the cervical spine of female patients suffering from ankylosing spondylitis usually shows synodesmophytic formations and ankylosis of apophyseal joints. Such alterations were observed by Resnick et al. (42) in five out of a group of 16 female patients with the diagnosis of AS. Upon a similar examination of 55 males, isolated abnormalities were seen in the cervical spine region. Hart and Robinson (43) also observed more frequent clinical involvement of cervical spine in females affected by ankylosing spondylitis. Armstrong et al. (41) have speculated that the karyotype 47XXX and thus the X chromosome may play an important role in the expression of the disease. Some later references can be found in the literature to two cases of coincident ankylosing spondylitis and KS: papers by Coulomer et al. (44) and Pages et al. (45), who were the first to describe the association of the peripheral form of AS with KS. With respect to the pathogenesis of KS and autoimmune diseases, opinions converge in that a doubled chromosome X and a low androgens-to-oestrogens ratio are a typical feature of KS that may play an important role in the pathogenesis of
autoimmune diseases. Low testosterone levels found in patients with KS might be an appropriate background for a predisposition for the development of autoimmune diseases. It may therefore be appropriate to continuously monitor testosterone levels in autoimmune diseases and to compare them with the progression and outcome. Also, it appears that KS should be monitored from the aspect of the development of autoimmune diseases, as it is associated with hypogonadism. It appears that the syndrome could be an appropriate background on which autoimmune diseases might develop.

**DISCUSSION**

With respect to the pathogenesis of KS and autoimmune diseases, opinions converge in that a doubled chromosome X and a low androgens-to-oestrogens ratio is a typical feature of KS that may play an important role in the pathogenesis of autoimmune diseases. Low testosterone levels found in patients with KS might be a predisposing factor for the development of autoimmune diseases. It may therefore be appropriate to continuously monitor testosterone levels in autoimmune diseases and to compare them with the progression and outcome. Also, it appears that KS should be monitored from the aspect of the development of autoimmune diseases, as it is associated with hypogonadism.

Psychology is another story: as in some other pathological conditions determined by chromosomal aberrations, mental disturbances are observed in KS. As a rule, deficit of intellectual capacities is associated with the superfluous chromosome X. Although cases without retarded mental development have been reported as well, even cases with above-average intelligence, these can only be considered as exceptions. Generally, reduced performance is usually observed in such patients, including reduced ability to perform physically, reduced level of aspirations, disharmonic personality, disturbed social adjustment, etc. These features were also present in our patient.

Deterioration of mental capacities and behaviour implies a number of problems in the social and personal life of the affected person. Useful services may be provided by systematic, biodromal psychological counselling (at school, occupational, premarital, marital) as well as long-term psychotherapeutical and/or psychagogic care whose role it is to strengthen the patient’s motivation system, the shaping of the patient’s relation to the other gender, to occupation as well as to the social environment in general.
Podáva sa prehľad výskytu Klinefelterovho syndrómu so zápalovými reumatickými chorobami, s reumatoidnou artritídou, s juvenilnou idiópatickou artritídou, s psoriatickou artritídou, s polymyozitídou/dermatomyozitídou, so systémovým lupus erythematosus, so systémovou sklerózou, so zmiešanou chorobou spojivoveho tkáníva, s antfosfolipidovým syndrómom a s ankylozujúcou spondylitídou. Uvádzajú sa aj vlastné pozorovania koexistencie Klinefelterovho syndrómu s reumatoidnou artritídou a antisynthetázovým syndrómom. Venuje sa pozornosť patogenéze a priebehu ochorenia pri Klinefelterovom syndróme. Poukazuje sa aj na včasnú diagnostiku tohoto syndrómu v koexistencii so systémovými chorobami spojiva.

REFERENCES


