Rare Genetic Disorders in Rheumatology

The majority of diseases seen in rheumatological practice are the result of the interaction of multiple genes with each other or with combinations of environmental and external factors. This article will outline a selection of chromosomal and rare single-gene disorders. In the universe of health care, each of these diseases is numerically insignificant, but viewed as a heterogeneous group, they are not uncommon. They are important because incorrect or delayed diagnosis may be detrimental, especially if there is simulation of common diseases, and specific musculoskeletal complications of genetic disorders such as Down syndrome must be recognized promptly by the consultant rheumatologist.

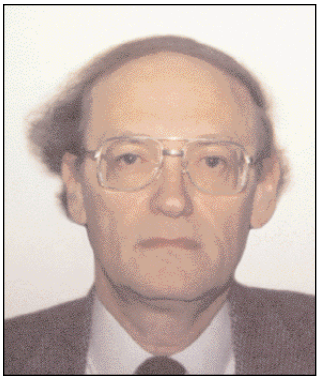
CHROMOSOMAL ABNORMALITIES

***Turner syndrome* (45,X).** Autoimmune diseases including thyroiditis occur with increased frequency. Juvenile arthritis may be six times more common than in the general population, with both oligoarticular and polyarticular patterns.[1] This association is unexplained and interesting because of the increased frequency of autoimmunity in normal (46,XX) females compared with males.

***Kleinfelter syndrome* (47,XXY).** Lupus is seen with unexpected frequency, and it is still not clear whether this is because of hormonal influence or other gene dose effects.

***Down syndrome* (trisomy 21)** is usually recognized early in life, but recognition of musculoskeletal complications may be delayed. These include articular hypermobility–associated problems at the atlanto-axial, hip and patello-femoral joints, and hyperuricemia with early-onset gout.

Velocardiofacial syndrome. Phenotypes associated with deletions of the long arm of chromosome 22 include DiGeorge and Shprintzen syndromes. Thymic hypoplasia is associated with abnormalities of T-cell maturation and function. Erosive polyarthritis[2] in young children is associated with developmental delays or learning disabilities, facial dysmorphism, gastro-oesophageal junction disorders and congenital heart defects.



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RARE SINGLE-GENE DISORDERS ASSOCIATED WITH ARTHRITIS

Abnormalities of apoptosis. Mutations of the Fas gene and the Fas ligand genes are associated with the autoimmune lymphoproliferative syndrome of lymphadenopathy, hepatosplenomegaly, finger clubbing, hyperglobulinemia, thrombocytopenia, and hematologic aberrations.

The presentation may resemble systemic-onset juvenile arthritis. Mouse strains with reduced capacity for Fas and Fas-L-induced apoptosis develop arthritis, nephritis and other autoimmune disorders.[3]

Periodic fever. Familial Mediterranean fever can simulate systemic onset juvenile arthritis, especially in children of Armenian, Turkish, Arab or Jewish ancestry. There are episodes of fever, abdominal pain, pleurisy and arthritis, skin rash, raised ESR but no leukocytosis. Amyloidosis, orchitis and vasculitis are important complications.[4]

RARE DISEASES OF CONNECTIVE TISSUE

Stickler syndrome, also known as hereditary arthro-ophthalmopathy,[5] causes premature osteoarthritis in large joints and vitreo-retinal disease. Type II collagen was identified in cartilage and the vitreous, then its "candidate gene," was confirmed as the culprit in most Stickler syndrome kindreds. The gene for another cartilage collagen, Type XI is abnormal in Type II Stickler syndrome, where there are skeletal and articular, but not ophthalmic abnormalities.

Marfan syndrome should be recognised from the long digits and limbs, anterior chest deformity, poor muscle mass and abnormalities of the ocular lens or aortic root. Thirty percent of patients have sporadic new mutations in the FBN1 gene, and will not have a family history. In addition, many FBN mutations do not produce the textbook phenotype. Once suspicion has been raised, the threshold for ordering an echocardiogram should be low. Numerous fibrillin mutations make molecular diagnosis difficult unless there are several Marfan patients in the family.

OSTEOCHONDRODYSPLASIAS RESEMBLING INFLAMMATORY ARTHRITIS

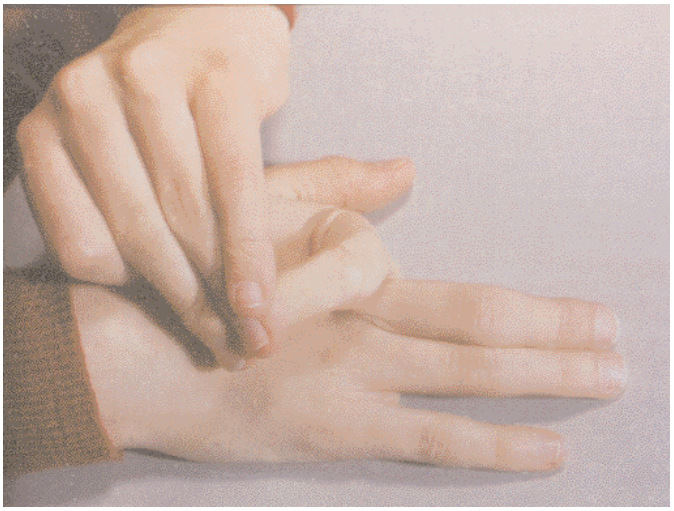
Progressive pseudorheumatoid dysplasia is a curious autosomal recessive disorder presenting in the first decade with pain and swelling of small and large joints, effusions, cartilage thickening or erosion, but no inflammatory findings in flood or synovial fluid.[6] This is one of several pseudo-inflammatory syndromes including familial hypertrophic synovitis and camtodactyly-arthropathy-pericarditis syndrome,[7] in which mutations of connective tissue proteins in growing joints give rise to simulation of inflammatory arthritis.

METABOLIC DISORDERS

Most inborn errors of metabolism are transmitted as autosomal recessives with low-gene frequencies, and therefore they are more common in some ethnically homogenous populations. An example is aspartylgluosaminouria, a glycoprotein degradation syndrome reported in remote areas of Finland; it causes saggy skin, facial dysmorphism and an erosive polyarthritis may start in childhood.[8] Better known in rheumatology is Lesch-Nyhan syndrome, in which gout and renal damage may develop in teenage boys.[9]

CONCLUSION

Viewed from the scientific aspect, these "experiments of nature" inform us about the physiology of the same tissues that become damaged in everyday rheumatic diseases. From the clinical aspect, the diversity of clinical phenotypes, and their variation with age of the child, offer a distinctive challenge to the skills of the pediatric rheumatologist.



Ehlers Danlos type I patient

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