SYMPTOMS AND SIGNS: Marinesco-Sjögren syndrome is usually evident at birth because of hypotonia. The cataracts are often not present at birth but may appear rapidly during childhood. Motor milestones are significantly delayed, with ataxia becoming noticeable by the time the child can sit. Most affected individuals are eventually able to ambulate with a walker. Linear growth is poor, and pubertal development may not occur because of hypergonadotropic hypogonadism. Mental retardation is generally mild to moderate in severity. Neurologic deterioration is slow to absent, and prolonged survival is possible, but the muscle weakness tends to be progressive. Less commonly reported features include optic atrophy, brachydactyly, and cone epiphyses.

ETIOLOGY/EPIDEMIOLOGY: Marinesco-Sjögren syndrome is inherited as an autosomal-recessive trait with complete penetrance in both sexes. The genetic defect is unknown. More than 100 cases have been reported. It is panethnic, but rare except in genetic isolates in rural areas.

DIAGNOSIS: The diagnosis should be suspected based on the clinical symptoms. An ophthalmologic examination (cataracts) and MRI of the brain (cerebellar atrophy, particularly involving the vermis) can be helpful. Muscle biopsy findings are generally nonspecific, although ragged red fibers and abnormal mitochondria have been reported. Multilamellar inclusions can be present in muscle and conjunctival biopsy samples as well as in cultured fibroblasts. Results of metabolic testing are normal.

TREATMENT

Standard Therapies: Treatment is supportive and based on symptoms. Removal of the cataracts and placement of a lens implant is often required to preserve vision. Physical and occupational therapy and special education are helpful. Hormone replacement therapy is needed if hypogonadism is present.

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RESOURCES

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22 Nail-Patella Syndrome

Elizabeth Sweeney, MB, ChB, and Iain McIntosh, PhD

DEFINITION: Nail-patella syndrome (NPS) is a genetic condition affecting the nails, patellae, elbows, and kidneys. There is also a risk of glaucoma. The severity is variable from person to person, even within the same family.

SYNONYMS: Onycho-osteodysplasia; Hereditary osteo-onychodysplasia; Fong disease; Turner-Kieser syndrome; Österreicher-Turner syndrome.

DIFFERENTIAL DIAGNOSIS: Small patella syndrome (ischiopatellar dysplasia); Patella aplasia-hypoplasia; Anonychia.

SYMPTOMS AND SIGNS: The fingernails are affected in 98% of patients in a characteristic manner. The thumbnail is the most severely (and may be the only) affected nail, and the severity of nail involvement decreases toward the fifth finger. Nails may be absent, small, thin, ridged, or split. Some nails may have a longitudinal ridge of skin running through the middle. The lunulae of the nails are often triangular. The toenails are involved in half of patients, typically with a small, dystrophic little toenail, but other nails may be thickened or discolored. There is often loss of the skin creases overlying the distal interphalangeal joints of the fingers, and there may be clinodactyly of the fifth finger and hyperextensibility of the finger joints with swan necking. Pes planus is a frequent occurrence, and congenital talipes is common. The Achilles tendons may be short, leading to toe-walking, and tight hamstring tendons may limit knee extension. The patellae are prone to lateral dislocation. Most patients have hypoplastic patellae; some patients have absent patellae. Most patients have some loss of elbow extension, and often limited pronation and supination of the elbows occurs. Some may have elbow pterygia. The shoulders and hips may also be affected. Back pain occurs in half

of patients and may be severe. There may be an increased lumbar lordosis and occasionally spondylolisthesis or vertebral defects. Radiographs of the pelvis show iliac horns in 70% of patients. Renal involvement may be clinically detectable in 30% of patients and may manifest at any age. Renal disease may progress to renal failure in a minority of patients. Raised intraocular pressure or glaucoma affects approximately 20% of patients and may develop at a younger age than in the general population. Irritable bowel syndrome and chronic constipation are more common in patients with NPS. The incidence of Raynaud phenomenon, of paraesthesia of the hands and feet, and of weakened teeth is increased.

ETIOLOGY/EPIDEMIOLOGY: The syndrome is caused by mutations in the gene *LMX1B,* which is located on chromosome 9 at 9q34. *LMX1B* is essential for dorsoventral patterning of the developing limb, regulation of collagen expression in the glomerular basement membrane, development of the anterior chamber of the eye, and differentiation of dopaminergic neurons. The incidence is estimated at 1 in 50,000 people, but this may be an underestimate. The syndrome has been reported in all ethnic groups, and is inherited in an autosomal-dominant manner. Approximately 15% of cases may be the result of a new *LMX1B* mutation, with neither parent being affected.

DIAGNOSIS: Diagnosis is made on clinical features, although gene testing may be of help in difficult cases. Prenatal diagnosis may be possible in the first trimester by means of molecular analysis of a chorionic villus sample.

TREATMENT

Standard Therapies: No specific treatment exists, but joints may benefit from individualized physiotherapy or surgery. Because the joint anatomy is abnormal in NPS, MRI scanning is recommended before physiotherapy or surgery. Particular attention should be directed to the muscle attachment points, because there may be wide variation from normal. Glaucoma may be treated in the standard manner, and kidney involvement may require medical treatment or occasionally dialysis or transplantation. Proteinuria may be controlled using angiotensin-converting enzyme inhibitors. Kidney function should be carefully monitored during pregnancy. It is recommended that patients have yearly urinalysis from birth and regular ophthalmologic examinations to diagnose glaucoma as early as possible.

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RESOURCES

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23 Noonan Syndrome

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DEFINITION: Noonan syndrome is an autosomal-dominant multiple congenital anomaly syndrome. Features are variable and include short stature, congenital heart defect, broad or webbed neck, chest deformity with pectus carinatum above and pectus excavatum below, developmental delay, undescended testicles, and a characteristic facial appearance.

DIFFERENTIAL DIAGNOSIS: Cardiofaciocutaneous syndrome; Costello syndrome; Multiple lentigines (LEOPARD) syndrome; Watson syndrome; Williams syndrome; Aarskog syndrome.

SYMPTOMS AND SIGNS: The facial appearance of Noonan syndrome is most distinctive in newborns and in middle childhood; it is difficult to recognize in adults. In the neonate, features include a tall forehead, wide-spaced and down-slanting eyes, low-set posteriorly rotated ears with a thickened rim, a well-grooved upper lip, and short neck with excess skin. In infancy, eyes are prominent and lids may be droopy or thickened. The nose has a depressed root, with a wide base and bulbous tip. In childhood, there may be apparent lack of expression or droopy, myopathic appearance. By adolescence, features are fine and the face has lengthened, becoming broad at the temples and tapering down to a small, pointed chin. The neck lengthens, creating a broad or webbed shape. The chest shape is un-