Diagnostic Principles
For a clinical diagnosis of Marfan syndrome, in the absence of family history, an affected person should display major criteria in at least two organ systems (cardiac, eye, skeletal, dural ectasia) and involvement of a third organ system. In the presence of a positive family history, an affected person should display one major criterion in an organ system and involvement of a second organ system. Inability to detect a mutation in FBN1 or molecular abnormality of fibrillin-1 does not exclude the diagnosis of Marfan syndrome in a person who fulfills the clinical criteria.

Therapeutic Principles
Early recognition and diagnosis of Marfan syndrome is important in order to enable implementation of treatment for cardiovascular symptoms. Beta-adrenergic blockers such as atenolol are used to decrease the rate of aortic root enlargement. Prophylactic repair of thoracic aneurysms is recommended when the diameter reaches between 5.0 and 5.5 cm. Patients should avoid contact sports and isometric exercise in order to minimize shearing forces on the aorta. Periodic ophthalmologic and orthopedic follow-up are necessary. Surgical correction of scoliosis may be necessary. As patients with Marfan syndrome survive longer, it is anticipated that degenerative arthritis of the hip, knees and other joints will represent new health concerns.

References

Marie-Strumpell Spondylitis
▶ Ankylosing Spondylitis

Marinesco-Sjögren Syndrome

Inga Harting1, Nicole I. Wolf2
1Department of Neuroradiology, University of Heidelberg Medical Centre, Heidelberg, Germany
2Department of Pediatric Neurology, University of Heidelberg Medical Centre, Heidelberg, Germany

Synonyms
MSS; Hereditary congenital spinocerebellar ataxia accompanied by congenital cataract and oligophrenia

Definition and Characteristics
Marinesco-Sjögren syndrome (MSS; OMIM 248800) is a rare, clinically defined disease entity characterized by the triad of ataxia, bilateral cataracts which have been observed to occur with a variable, early childhood onset, usually after the age of 3, and nonprogressive psychomotor retardation. Frequent additional findings include muscle hypotonia, muscle weakness, muscular atrophy, as well as short stature. Endocrinological abnormalities as hypergonadotropic hypogonadism have been found in a number of patients.

Laboratory investigations may reveal a slightly increased level of creatine kinase. The most common findings on brain imaging are cerebellar hypoplasia or atrophy, more pronounced in the vermis than the hemispheres. At least three syndromes with additional, untypical features have been identified and separated from the characteristic MSS, namely the syndrome of congenital cataracts, facial dysmorphism, and neuropathy (CCFDN; OMIM 604168), a syndrome with additional demyelinating neuropathy and recurrent episodes of myoglobinuria/acute rhabdomyolysis, and MSS with chylomicron retention disease and low vitamin E (OMIM 607692).

Prevalence
Data on prevalence are missing. The disease is very rare.

Genes
The pattern of inheritance with healthy parents, manifestation in both sexes, and the frequently reported
consanguinity implies an autosomal recessive disease. Homozygosity mapping localized a MSS locus on chromosome 5q31 and recently mutations in SIL1 have been identified in patients with classical MSS. SIL1 encodes a nucleotide exchange factor for the heat-shock protein 70 (HSP70) chaperone BiP, a key factor in regulating endoplasmatic reticulum functions. Classical MSS has therefore been proposed to represent a disorder of protein biosynthesis or processing in the endoplasmatic reticulum.

In contrast, linkage analysis in CCFDN and in MSS with demyelinating neuropathy and myoglobinuria localized to a 18qter region. CCFDN is caused by mutations in the gene coding for a protein phosphatase, CTDP1. MSS with chylomicron retention disease is due to mutations in SARA2 on chromosome 5q31.1 involved in intracellular trafficking of proteins.

**Molecular and Systemic Pathophysiology**

Following the identification of a gene locus, classical MSS is currently thought to represent a disorder of protein biosynthesis or processing, though the underlying pathophysiology remains yet to be elucidated.

In the two reported cases with postmortem investigations, the most striking single abnormality was severe cerebellar atrophy. Histopathology of the cerebellum in a 4-year old boy demonstrated very severe atrophy of the cortical ribbon with almost complete absence of Purkinje and granule cells while cerebellar foliation was normally preserved. Nerve fibers were nearly completely lost in the cortex and severely reduced in the cerebellar white matter; in addition, gliosis of the cerebellar nuclei was noted. Atrophy and gliosis were also observed in pontine nuclei, transverse pontine fibers and descending tracts, as well as the inferior olivary nuclei. Biopsied muscle reveals a unique dense double membrane structure associated with the nuclei on electron microscopy. Less specific myopathic changes include variation in fiber size, internalization of nuclei, autophagic vacuoles, and accumulation of abnormal mitochondria in a subsarcolemmal localization.

**Diagnostic Principles**

Diagnosis is based on typical clinical findings as described earlier. Mutation analysis of SIL1 confirms the diagnosis, as well as the presence of autophagic vacuoles and demonstration of unique dense membranous structures associated with cell nuclei in biopsied muscle.

**Therapeutic Principles**

Therapy is supportive with operation of cataracts to restore/preserve vision and physiotherapy to prevent contractures.

**References**


**Maroteaux-Lamy Syndrome**

▶Mucopolysaccharidoses

**Mastocytosis**

JÜRGEN GRABBE
Department of Dermatology, Medical University of Luebeck, Luebeck, Germany

**Definition and Characteristics**

Mastocytosis is an heterogeneous group of disorders characterized by primary increase of tissue mast cells especially in skin and bone marrow. According to different patterns of organ involvement, five main categories are defined: (i) pure cutaneous mastocytosis (e.g., urticaria pigmentosa), (ii) systemic mastocytosis, especially of the bone marrow, without concomitant hematological disorder, (iii) mastocytosis with an associated clonal hematological, non-mast cell lineage disease, (iv) high-grade leukemic mast cell disease, and (v) unifocal mast cell sarcoma [1]. Clinical symptoms of mastocytosis are due to increased mast cell burden and release of mediators both in allergic reactions or even in the absence of immunological stimulation: e.g., histamine, prostaglandins and leukotriens are responsible for urticaria, dyspnoe, diarrhea and hypotension. A generally increased overall releasibility of mast cells is not definitively proven in mastocytosis.