Charcot-Marie-Tooth Disease

Charcot-Marie-Tooth disease (CMT) also known as **Charcot–Marie–Tooth neuropathy** is a heterogeneous group of disorders characterized by distal muscle weakness and atrophy and loss of sensation in the feet and/or hands. Usually, the initial symptoms are foot deformities, such as high arches and hammertoes and “inverted champagne bottle” appearance of the lower parts of the legs. Weakness and muscle atrophy may occur in the hands as the disease progresses. Other symptoms of the disease may include hearing loss and scoliosis.

Prevalence of CMT hereditary neuropathy is about 1:2500.

Based on clinical manifestations and affected genes, CMT can be divided into types and subtypes. The most common form of CMT is **Charcot-Marie-Tooth type 1A** caused by duplication of or mutation in the **PMP22 gene**.

CMT neuropathy can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Carrier testing for at-risk family members
3. Genetic counseling

Cornelia de Lange Syndrome

Cornelia de Lange syndrome (CdLS) is characterized by distinctive facial features, growth retardation, developmental delay, hirsutism, and limb abnormalities. Craniofacial features include synophrys, arched eyebrows, long eyelashes, small upturned nose and thin downturned lips, small widely spaced teeth, and microcephaly.

Additional findings may include cardiac defects, gastrointestinal dysfunction, hearing loss, myopia, seizures, cleft palate, and cryptorchidism or hypoplastic genitalia.

The prevalence of disorder is estimated at 1:50,000 for the classic form of CdLS. CdLS can be inherited in an **autosomal dominant** or **X-linked manner**.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Carrier testing of at-risk female relatives
3. Prenatal diagnosis for known familial mutation
4. Genetic counseling

Menkes Disease

Menkes disease is a disorder of copper metabolism characterized by growth failure, developmental delay and progressive neurodegeneration. Patients with Menkes disease may also present hair changes (short, sparse, coarse, twisted hair, and colorless or steel-colored), hypothermia, hypoglycemia, hypotonia, and seizures. Onset of Menkes disease typically begins in the neonatal period.

Menkes disease is caused by mutations in the **ATP7A gene**. The disorder is inherited in an **X-linked recessive** pattern.

The incidence of Menkes disease is estimated to be 1 in 100,000 to 360,000 newborns.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Carrier testing for at-risk family members
3. Genetic counseling
4. Prenatal diagnosis for known familial mutation

Microcephaly

Microcephaly is a neurological condition characterized by occipito-frontal head circumference at birth equal to or less than -2 SD below the mean for sex, age, and ethnicity. Clinical findings may also include abnormal brain structure, cognitive impairment, short stature, craniosynostosis and seizures.

Microcephaly is considered primary, which is present at birth and secondary, which develops postnatally. Both **primary microcephaly** and **secondary microcephaly** can be isolated, syndromic or associated with other brain malformations. Genetic conditions with microcephaly involvement include**Cornelia de Lange syndrome**, **Seckel syndrome**, **Smith-Lemli-Opitz** syndrome, syndromes associated with chromosomal abnormatlities, and DNA repair disorders.

The inheritance patterns of microcephaly can be autosomal dominant, recessive or x-linked.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Differential diagnosis
3. Carrier testing for at-risk relatives
4. Prenatal diagnosis for known familial mutation
5. Genetic counseling

Mitochondrial Diseases

Mitochondrial diseases are a genetically and clinically heterogeneous group of disorders that arise as a consequence of dysfunction of the mitochondrial respiratory chain. The estimate for the prevalence of all mitochondrial disorders 1:8500, but they are thought to be greatly under-diagnosed. Mitochondrial disorders can be caused by mutations of **nuclear** or **mitochondrial DNA** (mtDNA). If nuclear gene defects may be inherited in an autosomal recessive or autosomal dominant manner, mtDNA defects are transmitted only maternally. As the female could have heteroplasmic mtDNA mutations, which could be transmitted unequally to her offspring, the sibs could exhibit considerable clinical variability.

Symptoms of the mitochondrial disease can begin at any age. Mitochondrial disorders may affect a single organ (e.g. **Leber hereditary optic neuropathy**, LHON) or involve multiple organ systems (e.g.**Myoclonic epilepsy** with ragged-red fibers, MERRF). Common clinical features of mitochondrial disorder include, for example muscle weakness, exercise intolerance, trouble with balance and coordination, sensorineural deafness, impaired vision, seizures and learning deficits, cardiomyopathy, diabetes mellitus, stunted growth, and a high incidence of mid- and late pregnancy loss.

1. Diagnosis of patients with phenotype characteristic for mitochondrial disease
2. Diagnosis of patients with family history suggestive for mitochondrial disease
3. Genetic counseling of individuals with mitochondrial disease and affected family members

Genetic testing of mitochondrial disease may be carried out on:

> DNA extracted from blood (in case of suspected nuclear DNA mutations and some mtDNA mutations), or
> DNA extracted from muscle (in case of suspected mtDNA mutations as pathogenic mtDNA mutations may not be detected in DNA extracted from blood [2]).

Smith-Lemli-Opitz Syndrome

Smith-Lemli-Opitz syndrome (SLOS) is an autosomal recessively inherited multiple malformation syndrome due to an inborn error cholesterol synthesis – insufficiency of enzyme 7-dehydroxycholesterol reductase. The syndrome is characterized by intrauterine and also postnatal growth retardation, moderate to severe mental retardation, malformations in many organ systems (cardiovascular, urogenital, gastrointestinal and central nervous systems). The patients have a characteristic appearance: ptosis, polydactyly, syndactyly of the II and III toes on both feet.

The incidence of SLOS is 1:20,000-70,000. SLOS is associated with mutations in the **DHCR7 gene**.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Carrier testing for at-risk family members
3. Genetic counseling
4. Prenatal diagnosis

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a neuromuscular disorder characterized by muscle weakness and atrophy resulting from progressive degeneration and loss of the lower motor neurons in the spinal cord and the brain stem nuclei. The weakness is almost always symmetric and progressive. Poor weight gain, pneumonia, sleeping problems, scoliosis, and joint contractures are common symptoms of SMA.

Spinal muscular atrophy is divided into five subtypes (**SMA 0, SMA I, SMA II, SMA III, SMA IV**), distinguished by the age of onset and maximum function attained.

SMA is inherited in an autosomal recessive manner. Disease incidence rate is 4-10 per 100,000 live births.

Indications for genetic testing:

1. Differential diagnostics
2. Carrier testing for at-risk relatives
3. Prenatal testing for known familial mutations
4. Genetic counseling

Wilson Disease

Wilson disease (WD) is an autosomal recessive inherited disorder characterized by the toxic accumulation of copper in various organs including the liver, the cornea and the brain, causing damage therein. The disorder usually manifests in the second decade of life and the hepatic form usually appears earlier than the neurological form. Wilson disease is caused by mutations in the**ATP7B gene**.

Indications for genetic testing:

1. Confirmation of clinical diagnosis
2. Carrier testing for at-risk family members
3. Genetic counseling