Prognosis

ADHD generally responds to treatment, but there are often residual school difficulties. Improvement depends on age at diagnosis, associated intelligence, and the effectiveness of clinical follow-up.

Rett Syndrome

Definition/Epidemiology

Rett Syndrome is an X-linked dominant disorder caused by a mutation of the methyl-cytosine binding protein (MECP2), a transcriptional repressor. The prevalence in girls is 1/10,000. In boys, MECP2 mutations are lethal or result in severe encephalopathy.

Pathology

Girls with Rett syndrome have a characteristic constellation of behaviors, but there are no specific pathologic hallmarks. Microcephaly is typically seen, with reduced frontotemporal brain volume. The loss of MECP2 function prevents the protein from regulating gene expression during critical developmental periods in infancy.

Clinical Presentation

Patients with Rett syndrome develop normally during their first year then lose communication skills with deceleration of head growth. A classic feature is loss of hand function and stereotypic hand wringing. Seizures are common.

Diagnosis/Differential

Diagnosis is confirmed by mutational testing of the MECP2 gene. Other conditions that can cause a similar presentation include Angelman syndrome, mitochondrial disorders, and neuronal ceroid lipofuscinosis.

Treatment

Girls usually required ongoing medical management of seizures, along with therapy for their gross and fine motor delays. They receive long-term enrichment and support for their intellectual disability.

Prognosis

While girls survive into adulthood, most will not acquire speech or functional skills; they will remain dependent for their care.

Fragile X Syndrome (FX)

Definition/Epidemiology

X-linked disorder caused by expanded CGG triplet repeats (>200 CGG repeats) in the first exon of the fragile X mental retardation gene *(FMR1)*. Considered an X-linked recessive disorder, females can be symptomatic though they may have milder intellectual disability compared with male. FX is the most common genetic cause of mental retardation, affecting 1/4000 males and 1/8000 females.

Pathology

Boys with FX have a characteristic constellation of behaviors and clinical findings on examination, but there are no specific pathologic hallmarks.

Clinical Presentation

Children with FX syndrome present with mild-to-moderate social anxiety, shyness, distractibility, hyperactivity, stereotypic movements, and intellectual disability. They are generally diagnosed before school age. Children have a distinctive appearance: relative macrocephaly with a long narrow face, and prominent ears, pubertal macro-orchidism, soft skin, and joint laxity. Individuals with 55 to 200 CGG repeats (the "pre-mutation" range) develop ataxia and tremor and cognitive dysfunction (Fragile X associated tremor/ataxia syndrome, FXTAS) in adulthood, at a median age of onset of 60 years.

Diagnosis/Differential

Diagnosis is confirmed by testing for increased repeats in the FMR gene. Other etiologies of intellectual disability and autism can be mistaken for FX. Adults with FXTAS are often diagnosed with a variety of other conditions which may present similarly (e.g., parkinsonism, other ataxia syndromes, tremor).

Treatment

Treatment focuses on appropriate behavioral and educational services. In older individuals with movement disorders, the treatment is supportive.

Prognosis

Patients with FX respond to training and education over time, but their intellectual disability may make it difficult for them to live independently. FXTAS tends to cause, gradual, progressive neurologic deterioration over many years.

NEUROCUTANEOUS DISORDERS

Neurocutaneous disorders are congenital, often hereditary disorders characterized by pathognomonic cutaneous and central nervous system lesions that uniquely distinguish each disease. The most important of these syndromes are neurofibromatosis 1 and 2, tuberous sclerosis complex, and Sturge-Weber syndrome. One disorder, von Hippel-Lindau disease, is often included with the neurocutaneous syndromes though skin findings are generally absent. Many neurocutaneous disorders are associated with abnormal, non-cancerous growth of tissues often in a disorganized manner. There is considerable variability in the spectrum of clinical manifestations.

Neurofibromatosis 1 (NF1)

Definition/Epidemiology

Autosomal dominant disorder caused by mutation of the gene, *NF1*, that encodes the protein, neurofibromin. NF1 is characterized by altered skin pigmentation, tumors, and abnormalities of bones, connective tissue, and brain. This is a relatively common disorder occurring in 1/3500 individuals.

Pathology

Neurofibromin is a tumor suppressor gene, and loss of function can lead to dysregulated cell growth and differentiation, accounting for the variety of tumors—cutaneous neurofibromas, plexiform neurofibromas, and gliomas—that can occur in NF1.