Rett Syndrome – an update

Review

K. A. Jellinger

Institute of Clinical Neurobiology, Vienna, Austria

Received January 30, 2003; accepted February 10, 2003
Published online April 22, 2003; © Springer-Verlag 2003

Summary. Rett syndrome is a progressive, usually sporadic and rarely familial, disabling neurodevelopmental disorder with onset in early childhood presenting clinically with mental retardation, behavioral changes, late movement disturbances, loss of speech and hand skills, ataxia, apraxia, irregular breathing with hyperventilation while awake, and frequent seizures. It occurs almost exclusively in females with an estimated prevalence of 1 in 10–22,000 births and is considered a manifestation of defective brain maturation caused by dominant mutation of the MeCP2 gene encoding the transcriptional repressor methyl-CpG-binding protein 2 related to the Xq28 locus. Although many different mutations of this protein are being studied in humans and in mice, the molecular pathogenesis of this disorder remains unclear. Electroencephalography is abnormal in the final stages of the syndrome. Neuroimaging showing brain atrophy may be required for differential diagnosis that includes neurodegenerative and metabolic disorders. Neuropathology shows decreased brain growth and reduced size of individual neurons, with thinned dendrites in some cortical layers and abnormalities in substantia nigra (decreased neuromelanin content), suggestive of deficient synaptogenic development, probably starting before birth. Neurometabolic changes include reduced levels of dopamine, serotonin, noradrenalin, choline acetyltransferase (ChAT), nerve growth factors, endorphines, glutamate, and other amino acids and their receptor levels in brain. Current treatment includes symptomatic, anticonvulsive and physiotherapy.

Keywords: Rett syndrome, genetics, diagnostic criteria, neuropathology, biochemistry, differential diagnosis, pathogenesis.

Synonyms and historical annotation

The peculiar syndrome in childhood was originally described by Andreas Rett, an Austrian pediatrician in 1966 (Rett, 1966), and a Japanese group
reported similar cases in 1978 (Ishikawa et al., 1978), but the condition only became known worldwide, when Hagberg et al. (1983) reported 35 girls affected with autism, dementia, ataxia, and loss of purposeful hand use from Sweden, Portugal, and France.

**Epidemiology**

Rett syndrome (RS) (OMIM # 312750 RTT) occurs in various ethnic populations worldwide. Although it remains underrecognized, it is a leading cause of mental retardation in females, second only to Down syndrome, with an estimated prevalence of 1 in 10,000 to 22,000 female births, exceeding that of phenylketonuria by about twofold (Hagberg, 1995).

**Genetics**

Most of the RS cases are sporadic, but familial occurrence and striking concordance in monozygotic twins suggested an X-linked dominant inheritance with possible male lethality. Genetic mapping studies in familial cases identified an Xq28 locus (Ellison et al., 1992; Sirianni et al., 1995) that subsequently was shown to contain mutations in the MeCP2 gene, which encodes the transcriptional repressor methyl-CpG-binding protein 2 (Amir et al., 1999; Wan et al., 1999) (Fig. 1). This protein binds to methylated DNA and is likely to mediate the biological role of DNA methylation which may result in

![Fig. 1. Schematic diagram of MeCP2 gene mutations. Exons are shown in boxes, noncoding region in black, methyl-binding domain in dark grey, and transcriptional representation in light grey. Missense mutations are shown in circles above, truncating mutations below the gene. The latter include nonsense mutations (squares), frameshift mutations (triangles), and splicing mutations (oval). Recurrent mutations are lined together. CpG hot spot mutations are indicated by filled circles or squares. *Insertion of 3 hp in the frameshift mutation 1147del 170hp (modified from Amir et al., 2000)](source_url)