

## Rett Syndrome – an update

### *Review*

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**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

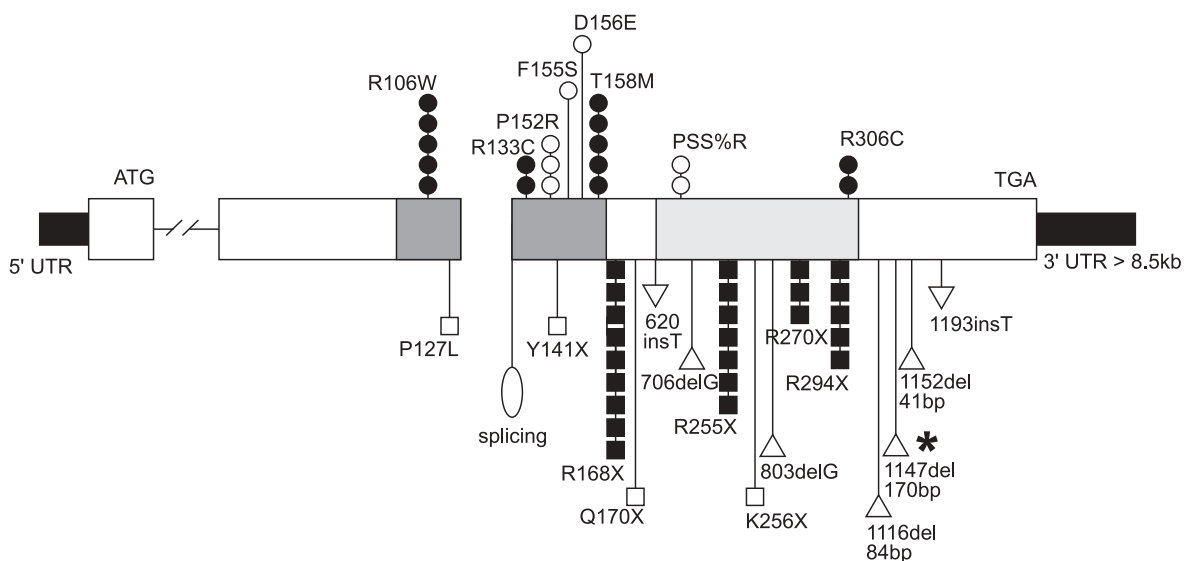
reported similar cases in 1978 (Ishikawa et al., 1978), but the condition only became known worldwide, when Hagberg et al. (1983) reported 35 girls affected with autism, dementia, ataxia, and loss of purposeful hand use from Sweden, Portugal, and France.

### Epidemiology

Rett syndrome (RS) (OMIN # 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 1147 del 170 bp (modified from Amir et al., 2000)

abnormal chromatin assembly or remodelling with consequent epigenetic effects on the expression of one or more not mutated genes (Bird and Wolfe, 1999). Nonsense or frameship mutations of MeCP2 gene and of the X-chromosome inactivation (XCI) pattern have been found in 80% of girls with classical RS, while almost no mutations were identified in RS families (Auranen et al., 2001; Van den Veyver and Zoghbi, 2002). Sixty-four percent of mutations are recurrent C > T transitions at eight CpG dinucleotides mutation hotspots, while the C-terminal region of the gene is prone to recurrent multinucleotide deletions (11%). Most mutations are predicted to result in total or partial loss of function of MeCP2. There is no clear correlation between the type and position of the mutation and the phenotypic features of classic and variant Rett syndrome patients, and XCI appears to be a major determinant of phenotypic severity (Van den Veyver and Zoghbi, 2002). Mutations in the amino-terminus are significantly correlated with more severe clinical presentation compared with mutations closer to the carboxyl-terminus of MeCPs (Hoffbuhr et al., 2001). An MeCP2 mutation can also be identified in boys, even though they do not present a RS phenotype (Villard et al., 2000). The infrequent occurrence of RS in boys has been explained by the existence of somatic mosaicism for an RS-causing MeCP2 mutation (Armstrong et al., 2001) and an Xq27–28 inversion and novel 32bp frameshift deletion (Hoffbuhr et al., 2001). Gene expression profiles in postmortem RS brain tissue were used to subcategorize individuals within the diagnostic group and to segregate them from controls (Colantuoni et al., 2001). Since specific mitochondrial DNA mutations have been identified in some RS patients, it has been speculated that RS may also result from such mutations. However, to date, there is no indication for a primary role of mitochondrial DNA mutations as a cause of RS.

### **Clinical features**

#### *Signs and symptoms*

The current guidelines for diagnosis of the classical RS are based on strict criteria summarised by the RS Diagnostic Criteria Work Group (Table 1). Growth and development before and shortly after birth are apparently normal and infants tend to reach “developmental milestones” at the expected rate and age. At the age of 3 to 6 months, stagnation of development and slowing of head growth are followed by regression, autistic-like behavior and stereotyped hand movements. Around the age of 6 to 18 months, diminished muscle tone (hypotonia), decreased eye contact, and inattentive behavior develop. Growth retardation/arrest with decrease of head circumference (acquired microcephaly) and decline in body weight after the age of 3 years result in a short stature by the end of adolescence. The disorder usually shows four stages with early onset (3–6 months), a regressive stage (1 to 4 years), relative stabilization, and late motor impairment (Table 2). Dystonia may be prominent and, in some older patients, rigidity and bradykinesia are present (Fitzgerald et al., 1990). The life span is diminished in RS, but despite growth and mental retardation, immobility, respiratory dysrhythmia (hyperventila-

**Table 1.** Diagnostic criteria for Rett Syndrome (modified from Hagberg et al., 1985 and Trevathan, 1988)*Necessary criteria\**

Apparently normal prenatal and perinatal period  
 Apparently normal psychomotor development within the first 6 months<sup>#</sup>  
 Normal head circumference at birth  
 Deceleration of head growth between ages 5 months and 4 years  
 Loss of acquired purposeful hand skills between ages 6 and 30 months, temporally associated with communication dysfunction and social withdrawal  
 Development of severely impaired expressive and receptive language, and presence of apparent severe psychomotor retardation  
 Stereotypic hand movements such as hand wringing/squeezing, clapping/tapping, mouthing and washing/rubbing automatisms appearing after purposeful hand skills are lost  
 Appearance of gait apraxia and truncal apraxia/ataxia between ages 1 and 4 years  
 Diagnosis tentative until 2 to 5 years of age

*Supportive criteria*

Breathing dysfunction  
 Periodic apnea during wakefulness  
 Intermittent hyperventilation  
 Breath-holding spells  
 Forced expulsion of air or saliva  
 Electroencephalographic abnormalities  
 Slow waking background and intermittent rhythmical slowing (3–5 Hz)  
 Epileptiform discharges, with or without clinical seizures  
 Seizures  
 Spasticity, often with associated development of muscle wasting and dystonia  
 Peripheral vasomotor disturbance  
 Scoliosis  
 Growth retardation  
 Hypotrophic small feet

*Exclusion criteria*

Evidence of intrauterine growth retardation  
 Organomegaly or other signs of storage disease  
 Retinopathy or optic atrophy  
 Microcephaly at birth  
 Evidence of perinatally acquired brain damage  
 Existence of identifiable metabolic or other progressive neurological disorder  
 Acquired neurological disorders resulting from severe infections or head trauma

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\* Female gender is no longer included, as the possibility of undiagnosed male cases can no longer be excluded (Villard et al., 2000). <sup>#</sup>Development may appear to be normal for up to 18 months

tion, periodic apnea), gastrointestinal dysfunctions (peristalsis, esophageal atony, obstipation, etc.), spasticity and joint contractures, and other life-threatening complications (e.g. arrhythmia due to cardiac transduction defects, and syncope), patients may survive into adolescence or even adulthood (Sekul and Percy, 1992).

Atypical forms or variants are frequent. They include girls with slowed development from the onset, maintenance of purposeful hand use, lack of

**Table 2.** Classic Rett Syndrome: clinical characteristics and differential diagnosis by stage (modified after Naidu, 1997)

Stage	Clinical characteristics	Differential diagnosis
<i>I. Early onset stagnation stage</i> Onset: 6–18 months	Development stagnation/arrest Deceleration of head/brain growth Disinterest in play activity Hypotonia Nonspecific personality changes Diminished play interest Hand waving – nonspecific, episodic	Benign congenital hypotonia Prader-Willi syndrome Cerebral palsy
<i>II. Rapid destructive stage</i> Onset: 1–3 years	Rapid developmental regression with irritability Poor hand use Seizures Hand stereotypies: wringing, Autistic manifestations Loss of expressive language Insomnia and irritability  Self-abusive behaviour (e.g., chewing fingers) Mental deterioration  Clumsy mobility/apraxia/ataxia Better preservation of gross motor functions Irregular breathing – hyperventilation	Autism  Psychosis Hearing or visual disturbance Encephalitis Infantile spasms (West syndrome) Tuberous sclerosis Ornithine carbamoyl transferase deficiency Phenylketonuria  Infantile neuronal ceroid lipofuscinosis
<i>III. Pseudostationary stage</i> Onset: 3–10 years	Severe mental retardation/apparent dementia Amelioration of autistic features Seizures and epileptic signs  Typical hand stereotypies Prominent gait ataxia and apraxia Jerky truncal ataxia Spasticity; gross motor dysfunction Hyperventilation, breath-holding, aerophagia Apnea during wakefulness Weight loss with excellent appetite Early scoliosis, Bruxism	Spastic ataxic cerebral palsy  Spinocerebellar degeneration Leukodystrophies or other storage disorders Neuroaxonal dystrophy Lennox-Gastaut syndrome Angelman syndrome
<i>IV. Late motor deterioration stage</i> Onset: 10+ years	Combined upper and lower motor neuron signs Progressive scoliosis, muscle wasting, and rigidity Severe multihandling syndrome Paraparesis or tetraparesis Decreasing mobility; wheelchair-bound Growth retardation, but normal puberty Impaired social interaction Staring, unfathomable gaze Emotional and eye contact “improving” Reduced seizure frequency Virtual absence of expressive and receptive language Trophic disturbance of feet Cachexia Respiratory abnormalities	Neurodegenerative disorders of unknown cause

stereotypies, or both, while others show early seizures with infantile spasms and later development of typical RS features. In others, the initial period of normal development is lacking, suggesting a precocious onset. *Formes frustes* show normal early development and regression at the age of 2–3 years but with less prominent developmental deviations, incomplete pattern of abnormalities and protracted clinical course. Few males with “RS-like” symptoms show developmental regression, loss of purposeful hand and finger movements, autistic-like behavior, loss of walking ability, progressive scoliosis, and seizures (Armstrong et al., 2001).

### *Imaging*

Cranial CT and MRI reveal usually normal findings in young patients, but slowly progressive generalized atrophy of both cerebral hemispheres and a disproportionate volume reduction in the caudate nucleus (Reiss et al., 1993), with global reduction of the gray and white matter volumes, particularly in the frontal and temporal regions, in the midbrain and cerebellum (Subramaniam et al., 1997). MRI studies of basal ganglia showed a significant reduction in the size of the caudate head and the thalamus (Dunn et al., 2002). Cerebral proton magnetic resonance spectroscopy (MRSI) shows decreased n-acetyl-aspartate (NAA) in both the grey and white matter particularly involving the frontal and parietal lobes and the insular cortex, reflecting reduced neuronal and dendritic tree size and also decreased neuronal function. Increased choline concentrations may result from gliosis (Gokcay et al., 2002; Horska et al., 2000) but there are no indications for mitochondrial disorders (Nielsen et al., 1993) and no correlations between spectroscopic changes and clinical status (Gokcay et al., 2002).

SPECT studies revealed hypoperfusion particularly in the prefrontal and temporoparietal regions with an association between early onset of the RS and the severity of reduced blood flow (Lappalainen et al., 1997; Burrioni et al., 1997). PET studies showed a reduction of fluorodopa (FD) uptake by around 13% in the caudate and putamen (Dunn et al., 2002), a significant reduction of dopamine transporter (DAT) protein in the caudate nucleus and putamen and low to low-normal density of postsynaptic dopamine D<sub>2</sub> receptors in the putamen (Wong et al., 1998). This was recently confirmed in elder RS girls (Dunn and MacLeod, 2001), while others (Chiron et al., 1993; Dunn et al., 2002) in younger RS patients had reported increased specific binding of D<sub>2</sub> receptors, suggesting that dopamine deficiency in RS leads to up-regulation of post-synaptic receptors. The number of dopamine D<sub>1</sub> receptors in the caudate nucleus and the density of dopamine reuptake sites in the cingulate and midfrontal cortex are unchanged, while the latter are decreased in the caudate nucleus and putamen (Wenk, 1995). These data suggest age-specific changes in the striatonigral dopaminergic system, with intact dopamine receptive neurons but increased activity of dopamine terminals. NMDA/glutamate receptors in the basal ganglia that are involved in activity-dependent plasticity and synaptic pruning are increased (Wenk et al., 1993). The binding protein (BP) for the benzodiazepine (BZD) receptor is significantly decreased in the

fronto-temporal, parietal, and occipital areas (Yamashita et al., 1998). A relative decrease in [F18]FD uptake in the lateral occipital area and a relative increase in the cerebellum were seen in both the younger and elder age group, while sensorimotor areas were preserved (Villemagne et al., 2002).

#### *Laboratory findings*

Routine laboratory studies including blood, urine, CSF, lysosomal enzymes, etc. have been unremarkable. Serum lactate and pyruvate levels are normal, while mild increase in CSF lactate and/or pyruvate levels may be associated with apnea and/or hyperventilation (Budden et al., 1990). Amino acid concentrations in serum, urine and CSF, dopamine, noradrenaline, adrenaline and serotonin in plasma and platelets, and monoamine oxidase B activity in platelets are within normal values (Riederer et al., 1986), while urinary excretion of biogenic amines and creatinine tends to be increased (Lekman et al., 1990). Assay of biogenic amines and their metabolites gave conflicting results showing either decreased levels of homovanillic acid (HVA), MHPG and 5-hydroxy indolic acid (5-HIAA) (Zoghbi et al., 1989; Ramaekers and Blau, 2001) or no significant changes of these metabolites (Lekman et al., 1990). Decreased CSF levels of 5-HIAA are accompanied by low levels of 5-methyltetrahydrofolate (5-MTHF) opposed by normal serum folate levels, while oral supplementation with folinic acid restored 5-MTHF values and serotonin turnover (Ramaekers and Blau, 2001). The CSF concentrations of gamma-butyric acid (GABA) and of other amino acids were normal (Perry et al., 1988), while glutamate was considerably elevated (Lappalainen et al., 1996). Decreased CSF levels of  $\beta$ -phenylalanine, an endogenous amine synthesized by decarboxylation of phenylalanine, may reflect impairment of the nigrostriatal dopaminergic system (Satoi et al., 2000). Plasma levels of  $\beta$  endorphin and prolactin are mildly decreased (Fanchetti et al., 1986), with increased CSF  $\beta$ -endorphin in some but not in all RS patients (Budden et al., 1990). CSF levels of substance P are decreased (Matsuishi et al., 1997). Biopterin, a cofactor in the synthesis of biogenic amines in blood and urine are normal, with mild decrease in CSF but no deficiency in the critical enzyme, dihydropteridine reductase (Zoghbi et al., 1989). Membrane cerebral lipids, e.g. gangliosides, are decreased in CSF (Lekman et al., 1991).

The electroencephalogram (EEG) is abnormal at various stages of the disease (Glaze et al., 1987; Hagne et al., 1989). The earliest abnormalities are noted during sleep, especially in the rapid eye movement (REM) stage (Segawa and Nomura, 1990), followed by slowing of the background rhythm with rare focal spike or sharp wave discharges or spike-wave complexes. At the age of 3 years, decrease in alpha 1 and increase in theta activity with a further decrease of alpha 1 and 2 and increasing theta activity are observed (Bashina et al., 1994). In stage III, variations in the amount of REM sleep and a general slow spike-wave pattern resembling the Lennox-Gastaut syndrome occur (Glaze et al., 1987). With advanced age, these changes tend to improve and ill-defined low-voltage records and rare epileptiform abnormalities may develop (Niedermeyer et al., 1990). Polygraphic studies show abnormal re-

spiratory patterns during wakefulness, and abnormal EEG with almost continuous spike- and wave-activity or epileptiform changes during sleep, which suggests an impaired voluntary behavioral respiratory control system (Kerr et al., 1990). Some RS patients show a distinct pattern of cortical reflex myoclonus with prolonged intracortical delay of the long-loop reflex and enlarged somatosensory evoked potentials (Guerrini et al., 1999).

After transcranial magnetic stimulation, in disease stages III and IV, short latencies for the onset of motor action potentials imply cortical hyperexcitability, with normal latency and duration of responses after cervical motor stimulation (Nezu et al., 1998). RS patients have lower than average visual acuity, but retinograms are normal (von Tetzchner et al., 1996). Hearing and the brainstem auditory pathway are intact, but the middle latency response is frequently abnormal, which suggests a central auditory dysfunction (Stach et al., 1994).

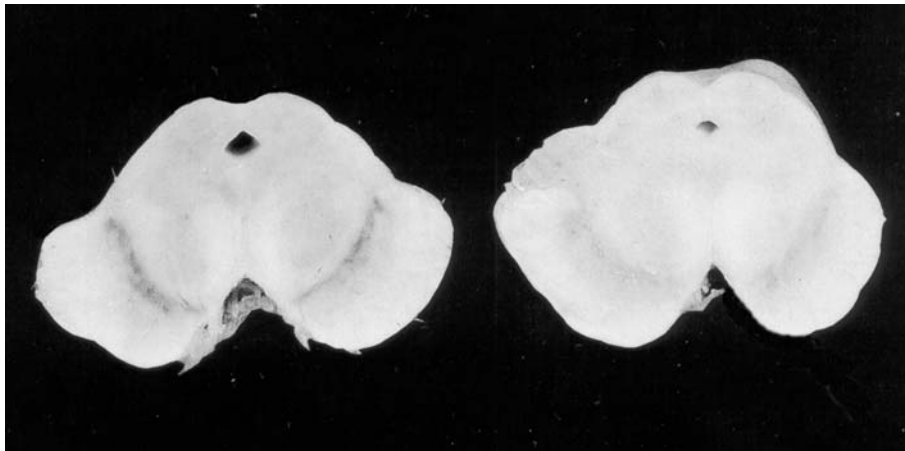
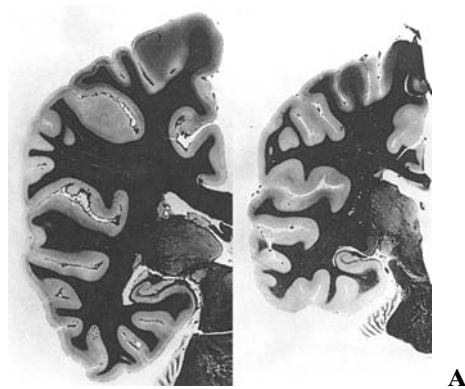
In early stages of RS, there is no sign of peripheral or spinal cord involvement, while prolongation of somatosensory evoked responses in older patients indicates involvement of the upper spinal cord and spinothalamic tracts (Bader et al., 1989): Nerve conduction studies also revealed evidence of axonopathy and denervation associated with lower motor dysfunction and limb atrophy (Jellinger et al., 1990).

### **Macroscopy**

Early decrease in head growth rate is followed by decrease in height and body weight with extremely small feet. At autopsy, all organs (excluding the lungs and adrenal glands) weight less than those of age-matched controls. The brain weight is reduced by 12 to 34%, with a mean in the range of 900 g, thus being lower than the 95% confidence limits of age-matched controls (Jellinger et al., 1988); it is not related to age, since there is no progressive decrease in brain weight after the age of 2.5 years (Armstrong, 1997). There is atrophy in the frontal and temporal regions, with reduction of the corpus callosum up to 30% (Reiss et al., 1993). Some RS brains show a pale substantia nigra (Fig. 2A,B) and gross atrophy of the cerebellum.

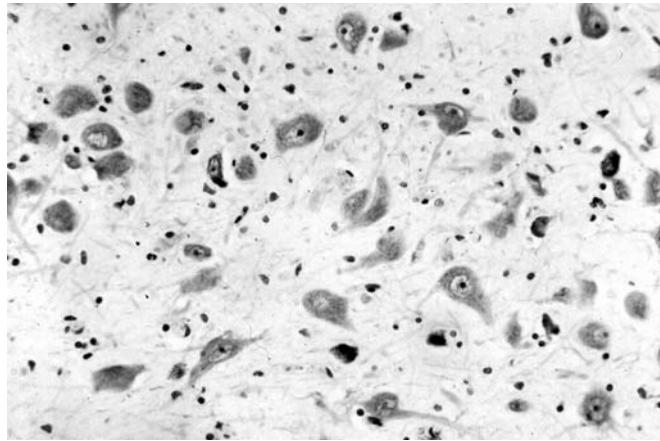
### **Histopathology**

There is a generalized reduction of neuronal size with increased cell-packing density in the cerebral cortex, thalamus, basal ganglia, amygdala, and hippocampus (Bauman et al., 1995). Other studies revealed a decline in neuronal numbers in the frontal and temporal cortex without decrease in cortical thickness, primarily involving the large pyramidal cells, more prominent in layers II and III than in the deep layers, and preservation of the visual cortex (Belichenko et al., 1994). These changes are associated with a lack of area specialization in the orientation pattern of dendrites and axons, decreased dendritic branching (Armstrong, 1997), small neurons with increased neuronal packing (Armstrong, 2002), losses of dendrites of pyramidal cells in frontal, motor, and subicular areas (Cornford et al., 1994), shortening of the apical and basilar dendritic branches in layers 3 and 5 of the frontal, motor,



**Fig. 2.** **A** Coronal section through cerebral hemisphere from control (left) and RS (right) brain both 21 years old, showing overall reduced size of RS brain. **B** The brainstem section of the RS case (right) is smaller and the pigmented region of the SN is thinner and paler than in the control (left)

and inferior temporal cortex (Armstrong et al., 1998), and “naked dendrites” without spines in pyramidal neurons, indicating a reduction in synaptic contacts from afferent neurons (Belichenko et al., 1997). Golgi studies showed a selective alteration in the size of dendrites of pyramidal neurons in the frontal, motor and temporal cortices, while the dendrites of pyramidal neurons in the hippocampus and visual cortex show no changes. Similar abnormalities characterize the medial temporal lobe structures in infantile autism (Bauman and Kemper, 1994). While there is an overexpression of lectin-stained perineuronal sets in the motor cortex, synaptophysin immunostaining shows a 20 to 40% area reduction in RS brain compared to age-matched controls involving all layers II and III in the frontal and motor regions (Belichenko et al., 1997). Most areas of the entorhinal cortex, fascia dentata, and hippocampus show cell hypochromia, chromatolysis or “ghost” cells in layers II and III with preservation of the cells in layers V and VI, whereas the CA 1 field of the hippocampus is normal (Leontovich et al., 1999). These data suggest a post-natal synaptogenic developmental deficiency, while the overexpression of

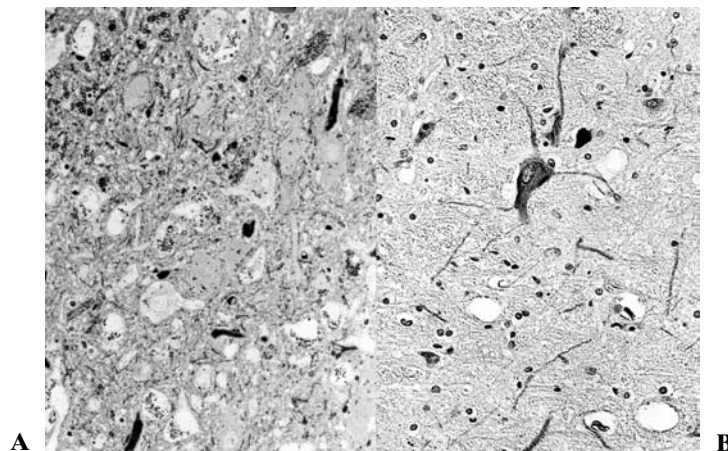


**Fig. 3.** Substantia nigra zona compacta of 15 year old RS girl showing normal number of neurons, most of which with no or only very little melanin pigment. Kresyl violett  $\times 50$

perineuronal networks in the cortex that develop in the early postnatal period and are fully expressed in the adult brain (Celio and Blumke, 1994) may be a morphological substrate of stabilization of existing synapses or of repelling of new synaptic contacts with the perikaryon and proximal dendrites.

Mild hypochromasia was observed in the striatum, and hyperchromia of large neurons in the striatum and internal pallidum, here with abnormal dendrites and degeneration of thick myelinated fibres (Belichenko et al., 1994; Leontovich et al., 1999), and mild diffuse gliosis.

Another conspicuous finding is a hypomelanation of the substantia nigra pars compacta without definite neuronal loss, a majority of large nigral neurons containing little or no neuromelanin (Jellinger et al., 1988; Kitt and Wilcox, 1995) (Figs. 3, 4). Only in one RS patient aged 21 years, nigral cells



**Fig. 4.** **A** Substantia nigra zona compacta of 15 year old RS girl. Semithin section showing small numbers of pigment granules in neurons. Toluidin blue  $\times 900$ . **B** Decreased number of tyrosine hydroxylase (TOH) immunoreactive neurons and fibres in substantia nigra of 17 year old RS girl. TOH immunohistochemistry  $\times 450$

were reduced by about 30% of age-matched controls, and the demonstration of free pigment granules in the neuropil as seen in Parkinson disease. These and preliminary data showing labeling of fragmented intranucleosomal DNA using the TUNEL method in SN neurons suggest that they undergo active degeneration (Kitt and Wilcox, 1995). No apparent abnormalities in other pigmented brainstem nuclei are seen, and morphometric studies of the serotonergic dorsal raphe nuclei showed no neuronal decrease, while reduced cell numbers were reported in the cholinergic nucleus basalis of Meynert (Kitt et al., 1990).

The cerebellum may show gross atrophy of all lobules of the vermis and progressive loss of Purkinje cells, with preservation of the basket and stellate cells independent of age (Oldfors et al., 1990), with simplification of the inferior olivary nucleus without cell loss or with gliosis. These findings also seen in infantile autism (Bauman and Kemper, 1994) suggest arrested development beginning before birth (Bauman et al., 1995).

In adult RS patients, axonal degeneration and gliosis in spinal cord tracts, loss of motor neurons and spinal ganglion cells have been observed (Oldfors et al., 1988).

Peripheral nerves are either unremarkable or show mild axonal neuropathy with degenerative or regenerative changes but without primary demyelination (Jellinger et al., 1990).

Muscle biopsies are either normal or show type II and type I atrophy in a few cases (Wakia et al., 1990) or mild myopathic changes (Armstrong, 1997).

The pathology of the autonomic nervous system has not been systematically investigated. The cardiovascular system shows no gross alterations, but serial sections through the AV nodes in several Rett hearts have revealed an immature dispersed arrangement of the muscle fibres in the conduction system (Armstrong, 1997).

### **Immunohistochemistry and electron microscopy**

Immunohistochemical studies revealed a reduced expression of microtubule-associated protein (MAP)2 in the neocortex, with a reversal of the normal pattern of more intense staining in the deep cortical layers and preservation of nonphosphorylated neurofilament (SM1) labeling of pyramidal neurons and calbindin-stained GABAergic neurons (Kaufmann et al., 1995). These data indicate a marked disruption of a major cytoskeletal component in RS neocortex. Since MAP-2 expression appears early in the neuronal maturation of the neocortex, these abnormalities may indicate developmental disturbances. While some studies showed no reduction of cortical levels of nerve growth factor (NGF) and p75 low-affinity receptor for NGF but significant reduction of choline acetyl transferase (ChAT)-positive neurons (Wenk et al., 1999), others found a significantly reduced expression of NGF and of its high affinity receptor *trkA*, which was significantly related to the presence of cortical astrogliosis (Lipani et al., 2000). There is a significant decline in the number of ChAT-containing neurons in the forebrain which, however, appears not caused by a lack of NGF but in the production of acetylcholine

(Wenk et al., 1999). Mildly reduced activity of tyrosine hydroxylase (TOH), the rate-limiting enzyme of catecholamine synthesis, was seen in nigral neurons, striatonigral loop fibers, and in some hypothalamic nuclei (Jellinger et al., 1988). The lack of MeCP2, the product of the causative gene of the RS, in specific periods and regions may lead to the dysfunction of catecholaminic and other neurons in Rett brain (Itoh and Takashima, 2002).

Autoradiographic studies found significant reductions in glutamate and GABA receptor density in the putamen and caudate nucleus of older RS cases, while mGluRe density was not altered significantly. In contrast to ionotropic GluRe, GABA receptor density was significantly increased in the caudate nucleus of young RS patients, demonstrating regional, receptor-subtype and age-specific alterations in amino acid neurotransmitter receptors in the basal ganglia (Blue et al., 1999). Substance P immunoreactivity is significantly decreased in the locus coeruleus, pontine nuclei and spinal cord, less severe in the substantia nigra, central gray of the midbrain, striatum, frontal cortex, and thalamus, also associated with increased astrogliosis (Deguchi et al., 2000). The hypothalamic-pituitary axis in older RS patients revealed reduced immunostaining of prolactin and growth hormone, while stainings for follicle and thyroid stimulating, luteinizing, and adrenocorticotropic hormones did not differ from those in controls (Jellinger et al., 1988). Decreased cytochrome c oxidase and succinate cytochrome c reductase activities have been noted in muscle biopsies of RS patients with normal muscle mitochondrial ultrastructure (Coker and Melnyk, 1991).

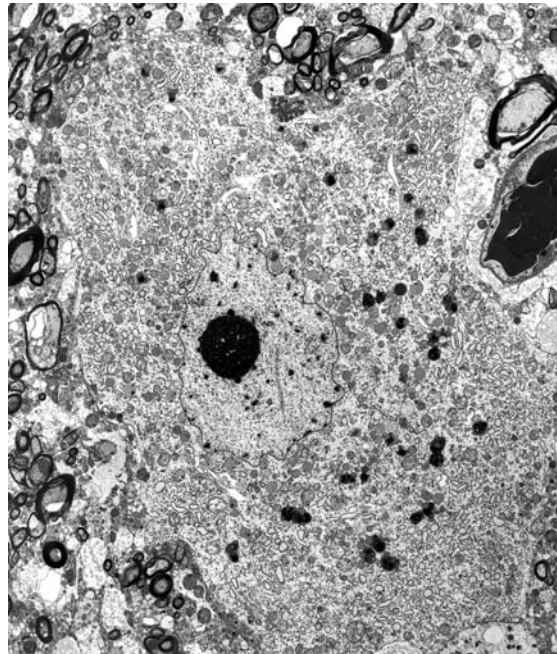
Electron microscopy revealed abnormal neurites, filled with lysosomes and laminate bodies in the frontal cortex and caudate nucleus with few axonal and dendritic connections, and axonal swellings packed with large mitochondria and membranous, multilamellar or zebra-like bodies, resembling reactive or degenerative axonal swellings (Fig. 6). Lamellated lipid-like bodies and intraneuronal liposomes containing lipofuscin-like materials have been observed in both biopsy and autopsy materials (Papadimitriou et al., 1988; Cornfort et al., 1994), but there are no other features of any lipid storage disorder. The ultrastructural appearance of neuromelanin in nigral neurons is normal (Fig. 5).

In muscle biopsies, abnormal, dumbbell-shaped mitochondria with foamy vacuoles were observed (Ruch et al., 1989).

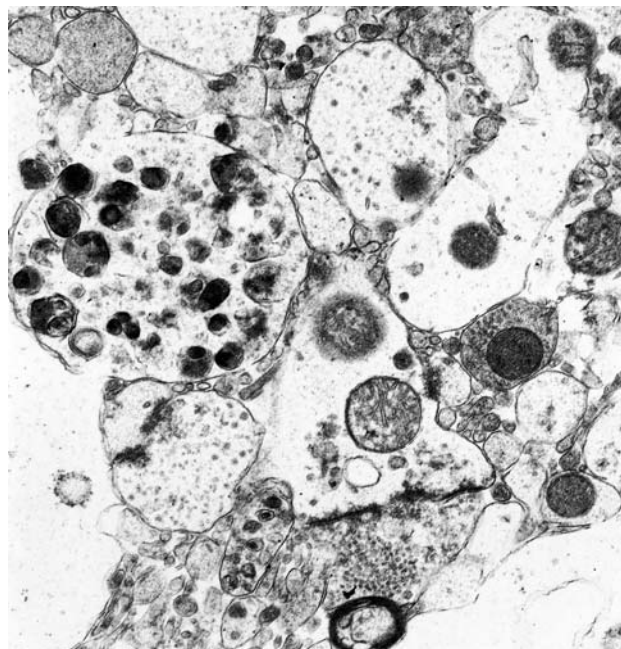
#### *Clinico-pathological correlation*

*Growth retardation:* Microcephaly and micrencephaly, i.e. reduced head circumference, brain volume and weight, are related to decreased numbers and density of neurons in the cortex, subcortical areas, and cerebellum caused by postnatal synaptogenic maturation arrest, which is associated with general growth deficits, the causes of which are still unknown.

*Mental retardation,* autistic behavior, and cognitive deficits may be related to architectural abnormalities and paucity of dendritic spines and decreased synapse density, and neuronal loss in cortical layers II and III of the frontal cortex due to deprivation of trophic inputs (Belichenko et al., 1997) and to



**Fig. 5.** Multipolar nigra neurone in 11 year old RS girl with regular cytoplasmic organelles but very few neuromelanin granules.  $\times 5.170$



**Fig. 6.** Isolated abnormal neurite packed with granular bodies and disintegrating mitochondria in the caudate nucleus. Adjacent well preserved axodendritic synapse and postsynaptic terminals are filled with dense core vesicles.  $\times 27.000$  (from Jellinger et al., 1988 – with permission)

dysfunction of the cholinergic forebrain system causing reduced cortical ChAT activity. Dysfunctions of the prefrontal cortex may contribute to the autistic features in RS (Akbarian et al., 2001).

*Movement disorders* may be related to dysfunctions of the central dopaminergic system documented by both morphological and biochemical studies.

*Gait and motor dysfunctions* could be attributed to dysfunctions of the cerebellar circuits, degeneration of corticospinal tracts, dorsal root ganglia and columns.

*Neuronal mosaicism* for normal and mutated MeCP2 produces a consistent phenotype in the classic female patient and a small brain with some preserved islands of function, but with an inability to support hand use and speech (Armstrong, 2002).

*Altered respiratory patterns* may be related to dysfunctions of central respiratory control and autonomic systems (Witt-Engerström and Kerr, 1998), while dysfunctions of the heart conduction system might be a possible explanation for sudden death (Guideri et al., 1999).

### **Biochemistry**

Postmortem studies showed reduced levels of dopamine, serotonin and their respective metabolites HVA and 5-HIAA in the substantia nigra of elder RS girls but no generalized deficiency of dopamine (Lekman et al., 1990), while others reported decreased levels of dopamine, norepinephrine, serotonin and their metabolites in most brain regions (Riederer et al., 1986; Wenk, 1997). Increased striatal dopamine/HVA ratio and elevated 3,4-dihydroxyphenylacetic acid indicate increased dopamine turnover in the brain, with reduced serotonin with regional increase of its precursor tryptophan in the striopallidum and substantia nigra (Lekman et al., 1990). A reduction of cortical ChAT suggests a dysfunction of the cholinergic forebrain system (Wenk et al., 1999).

Decreased ferritin, a major storage form of nonheme iron, in frontal cortex and striatum, indicating reduced iron binding, and reduced concentrations of glutathion and ascorbic acid suggest relationship to oxidative stress (Sofic et al., 1987), but no muscle electron transport defects or abnormalities of enzymes of the pyruvate metabolisms were found, and mitochondrial DNA studies from blood and muscle were all negative (Haas et al., 1995).

### **Differential diagnosis**

In the presence of the full spectrum of clinical features a definite diagnosis of RS can usually be made by the age of 2–3 years (Table 1). Authorities on RS have recommended revised inclusion criteria to allow for the diagnosis of atypical variants, including congenital onset, late regression, milder (forme fruste), and atypical male variants (Hagberg, 1995). The most common misdiagnosis is infantile autism showing many similar clinical and neuropathological features (see above). Differential diagnosis further includes

neurodegenerative and metabolic disorders shown in Table 2 that, however, can be distinguished by gene mapping, neuroimaging, biochemical, and other laboratory studies.

### **Experimental models**

Expression of the RS gene MeCP2 and of macrohistone H2A (MacroH2A) has been demonstrated ubiquitously in cortical neurons, including projection neurons and GABAergic interneurons in both monkey and mice. In the adult monkey, MeCP2 expression is robust throughout all layers of the prefrontal cortex, but it is limited in fetal monkeys at embryonic day 110 to deeper cortical layers and the subplate (Akbarian et al., 2001). These results suggest that MeCP2 may be important for neuronal maintenance in the developing and mature primate prefrontal cortex, consistent with the previously reported phenotype of MeCP2-null mutant mice (Chen et al., 2001). These, however, do not show behavioral symptoms until brain development is complete suggesting that MeCP2 may remain essential for maintenance of neuronal health beyond the developmental period (Guy et al., 2001). This conclusion is based on experiments with genetically engineered mice and it is yet unclear whether the findings can be extrapolated to the primate, including human brain.

### **Pathogenesis**

RS is often assumed as a postnatal phenotype manifestation of a prenatal developmental alteration (Naidu, 1997; Wenk, 1997). However, recent results are consistent with the hypothesis that MeCP2 is important for neonatal functions not only during the late phase of cortical development but also in the adult, after completion of maturation. MeCP2 expression was detectable in all neurons of fetal brain until 20 gestational weeks (GW). The expression disappeared in the cerebrum after 20GW and in the brainstem after perinatal or infantile periods, but re-appeared in the brainstem after adolescence. These findings suggest that the period and location of MeCP2 expression may play an important role in the pathogenesis of the RS. The lack of MeCP2 in specific periods and regions may lead to neuronal and synaptic dysfunction and dysfunction of catecholaminergic neurons in Rett brains (Itoh et al., 2002). The delayed occurrence of neurological disease in RS patients until several months after birth and the phenotype of adult, MeCP2 null-mutant mice (Guy et al., 2001) are consistent with this suggestion. At present, the underlying molecular pathology of MeCP2 deficiency remains unknown. Given its role as a methyl-CpG-binding protein and transcriptional repression, it is possible that loss of its function may result in an imbalance between gene transcription and gene silencing (Bird and Wolfe, 1999). Since overall brain morphology and cytoarchitectonics are preserved in both RS patients and MeCP2 mutant mice, a major developmental deficit as the underlying cause for RS is not likely, which, however, does not exclude a subtle developmental disturbance such as a defect in the formation of synaptic connections during the later phases of cortical development. MeCP2 is upregulated during

cortical maturation both in primate and in rodent, while high levels of MeCP2 expression in cortical neurons may play an essential role of chromatin remodeling in postmitotic neurons, but the basis of RS still await further elucidation.

### Treatment and future directions

The treatment of RS patients requires an integral, multidisciplinary approach including symptomatic and supportive medical management, physical, occupational, and speech therapy (Budden, 1997). Anticonvulsive medication (carbamazepine, valproic acid, lamotrigine) may help to reduce seizure activity. The benefit of dopaminomimetic drugs, e.g. L-dopa and dopamine agonists, is controversial, but may improve motor abilities (Zappella, 1990), while naltrexone, an opiate antagonist, may help to stabilize breathing irregularities (Percy et al., 1993). Administration of L-carnitine produced transient improvement (Plioplys et al., 1993). Since 5-HT1A receptors have been shown to effectively reverse stunted neurons and microencephaly produced in animal models of fetal alcohol syndrome and prenatal cocaine administration, the feasibility of treatment with 5-HT1A agonists in RS and other developmental disorders has been discussed (Azimitia, 2001). Implementation of a high-fat, high-caloric diet, delivery of liquid nutrients or gastrostomy feeding will be necessary in late stages of the disease. For RS patients with cardiac conduction defects (e.g., prolonged QT intervals), certain medications that may cause or aggravate the condition should be avoided. These may include certain antipsychotics such as thioridazine; tricyclic antidepressants; antiarrhythmics such as quinidine, sotalol, and amiodarone; antibiotics such as erythromycin; the antifungal agent ketoconazole; or other agents, such as cisapride, a stimulant of spontaneous gastrointestinal movement (GI motility). Symptomatic care is centered on orthopedic and physical therapy to improve balance, flexibility, and strengthen muscles, while speech and occupational therapy may improve patient interaction.

Future directions will be to exclude congenital metabolic defects and to further elucidate the causal relations between MeCP2 gene and the pathobiology of RS.

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