Original Article

Natural History of Rett Syndrome

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ABSTRACT

Rett syndrome is a unique neurodevelopmental disorder, with onset of hypotonia, autistic tendency, and abnormalities of fine finger movements and gross movements of the arms in early infancy. Clinical features include specific age-dependent symptoms. Studies of early and late signs correlated locomotive dysfunction to language disability and stereotypy to regression of higher cortical functions. Studies of sleep parameters revealed early hypofunction of brainstem aminergic neurons and late occurrence of hypofunction of dopaminergic neurons, followed by receptor supersensitivity. The syndrome's pathophysiology suggests that early hypofunction of aminergic neurons interferes with the development of higher neuronal systems. Particular symptoms surface at different ages throughout the natural course of Rett syndrome, with regressional and static periods. (*J Child Neurol* 2005;20:764–768).

Rett syndrome, named for Dr Andreas Rett, who first identified the syndrome, was originally assumed to be a progressive disorder.[1–3] This was because a child who has Rett syndrome appears to be normal for the first 6 to 18 months, with regression occurring during the course of the disease process, from late infancy to early childhood. A degenerative process in the central nervous system was suspected. However, clinical observation has shown that these children are not completely normal from very early infancy[4,5] and that the clinical status of some older patients becomes static. Neuropathologic studies have revealed no degenerative findings.[6,7]

Dr Rett organized the first symposium on Rett syndrome on April 8, 1983, in Vienna, Austria. A rather small group of people from Europe and Japan attended. In that meeting, Dr Rett described girls and women of various ages who had Rett syndrome. The similarities and dissimilarities of characteristic symptoms and signs according to patient age were obvious and striking. It was suggested that the natural course of the disorder depends on the developmental course of the central nervous system, which can be abnormal, with dysfunction of the central nervous system or hierarchically arranged neurons influencing the development of the various levels of the central nervous system. After carefully reviewing patient histories, we proposed that the disorder starts from early infancy, with dysfunction of brainstem aminergic neurons as the cause. However, it took some time before the disorder was widely recognized as a developmental disorder, and onset is much earlier than initially indicated.

Evaluating the natural history of Rett syndrome is important because initial symptoms indicate which neurons are primarily affected, and alterations of symptoms with age implicate the spreading of the involved neurons or neuronal systems or the neurons whose development is influenced by the neurons initially affected. Evaluation of abnormalities of sleep parameters and locomotion revealed abnormalities of the aminergic neurons of the brainstem and midbrain, which can cause malfunction of hierarchically arranged neurons of various levels.[8,9]

In this article, we review the natural clinical history of Rett syndrome and describe, on the basis of neurologic and clinical neurophysiologic studies, our hypothesis regarding its pathophysiology.

ONSET OF RETT SYNDROME

The most frequent presenting symptoms noted in our evaluation of patients with Rett syndrome were abnormalities of early development.[10] These abnormalities included mild placidity and frank delay of head control. However, most often the abnormalities that parents perceived were very subtle; parents stated that something was not right with their child or that their baby was very good, did not cry, and slept most of the day.[4,5] These clinical characteristics are the same as those observed in infants with infantile autism who show delayed development of the circadian sleep-wake rhythm and a poor response to environmental stimulation.[11] In late infancy, failure to crawl and deceleration of head growth are observed. In

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early childhood, rigid hypertonus, stereotypy, epileptic seizure, scoliosis, and loss of purposeful hand use appear.[2–4]

The neurophysiologic examination of sleep-wake rhythm and sleep parameters measured by polysomnography revealed the characteristic features that supported the underlying pathophysiology of age-dependent modification.[12,13] On the basis of these observations, we suggested that the onset of Rett syndrome was in early infancy. The syndrome's pathophysiology reveals that it is a developmental disorder caused by early dysfunction of brainstem aminergic neurons (ie, hypofunction of the serotonergic neurons [5-hydroxytryptamine] and the noradrenergic neurons).[4,14] Analysis of sleep parameters suggested abnormalities of the noradrenergic neuron, with critical age of development from 36 to 38 weeks' gestational age to 4 months' postnatal age, and hypofunction of the 5-hydroxytryptamine neurons, which activate antigravity systems by 4 months of age, and of the dopaminergic neurons, which occurs later and is followed by the appearance of receptor supersensitivity.[8,9]

CLASSIFICATION AND CLINICAL STAGING

Classic Rett syndrome affects girls and is defined by a normal prenatal and perinatal period (normal for the first 6 to 18 months).[15] Patients who do not meet the diagnostic criteria for the classic course are described as having one of the following forms of Rett syndrome: atypical, variant, forme fruste, congenital, early seizure, preserved speech, and male variant. In a British survey of 640 patients with Rett syndrome, 83% had the classic form and the rest were classified as atypical.[16]

In 1986, Hagberg and Witt-Engerström proposed four stages of Rett syndrome.[17] Stage I is from 6 months to 1½ years; patients are symptomatic but without apparent regression. Stage II is from 1 to 3 or 4 years and comprises a period of regression. Stages III and IV are after regression and are characterized as periods of stabilization, from preschool to adult ages and older. In 2001, the staging was modified by Kerr and Witt Engerström on the basis of the British survey and is summarized as follows: preregression, regression, and postregression.[16] These three periods are correlated to stage I, stage II, and stages III and IV by Hagberg and Witt-Engerström.[17] It was also said that preregression period starts much earlier than previously considered,[16,18] which was in accordance with our original proposal.[4,5]

AGE-RELATED ALTERATION OF SYMPTOMS

Early Infancy (First 6 Months)

It has been stressed that children with Rett syndrome appear to be normal in the initial 6 to 18 months of life; however, our analysis of motor milestones revealed that most showed delays in rolling over[10] and some in head control.[19] We evaluated the development of the motor milestones in 130 patients; 16% had delays in head control and 32% in rolling over. A retrospective questionnaire on the behavioral characteristics in infancy showed the babies to be quiet and placid. The delay in decrement of daytime sleep in late infancy to early childhood was also obvious. The placidity was attributed to the decrease in postural muscle tone.

The similar impression with regard to this period, such as undemanding nature, has also been pointed out by others.[16] Although detected only by careful history taking, abnormal excessive movements of the hands and fingers, habit-like movements of the hands and mouth, licking, or teeth grinding was present from early infancy.[16,19] An analysis of a home video from birth to 12 months revealed signs of potential difficulty in appearance, posture, movement, and contact. Researchers also reported some progress in the preregression period.[20,21] Abnormalities in generalized and fine finger movements were also pointed out during analysis of the home video (ie, detailed analysis of particular general movements for the first 4 months); none had normal general movements, and a specific abnormal general movement pattern was not detected, but they differed from movements associated with acquired brain lesions.[22]

Late Infancy to Early Childhood

Originally, late infancy to early childhood was the period believed to be associated with the onset of the classic form of Rett syndrome. This is the regression period, and babies who appeared to be normal were said to show rather sudden onset of autistic tendency.[23,24] Delay in motor milestones becomes apparent within months. The result of our evaluation with the same cohort of 130 cases showed a delay in the ability to sit in 41.2% (40 of 97 whose ages when they began to sit were known), to crawl in 63.6% (28 of 44 whose ages when they began to crawl were known; 71 never crawled), and to walk in 83.3% (55 of 66 whose ages when they began to walk were known). Speech delay became apparent. Losing purposeful hand use is observed at around 12 to 18 months, which is followed by pathognomonic hand stereotypies. After the occurrence of the stereotyped movements, some patients lost the ability to use words that they had previously attained, and other regression of symptoms became apparent. Toward early childhood, muscle hypertonus, starting from the legs, became apparent, and often the child showed pes varus or vulgus. Head growth began to decelerate after late infancy.

The precise pathomechanism of the regression is not known. The earlier onset of regression tends to be associated with a poorer outcome.[25] Similarly, the severity of the preregression period is also associated with the age at regression. In some cases, the regression period is not clear. In those patients, clinical features seem to be milder.

Childhood to Adulthood

Symptoms become stabilized in the period spanning from childhood to adulthood. Autistic features begin to disappear, and the child begins to associate with the environment. However, intellectual ability is severely affected. Motor symptoms seem to show slow progression. Dystonic muscle hypertonus increases, resulting in joint contracture. Scoliosis begins to slowly progress. Abnormal autonomic function, including breathing abnormalities, becomes evident. Epileptic seizures occur in some cases. However, during this period, a patient's overall condition typically stabilizes. The severity score seemed to rise until 15 years of age and to flatten at 25 years.

A British survey on death showed that in about half of the cases evaluated, patients died in a wasted condition, often around 15 to 20 years of age. The rest were from epileptic attack and from causes unrelated to the pathologic processes of Rett syndrome.[16] About a quarter of the deaths were sudden death and occurred without relation to a particular age. The annual death rate was shown to be 1.4% in Sweden and 1.2% in Britain.[16]

Late Adulthood to Old Age

In most cases, once a patient reaches adulthood, the condition stabilizes. If dementia progresses, muscle tone shows plastic rigidity and parkinsonism (but without tremor) seems to present. The scoliosis can stabilize in some. Often epileptic seizures decrease in frequency and severity. Overall clinical features become static.

Correlation of Early and Later Symptoms

The age-related clinical features of Rett syndrome reflect the underlying neuronal mechanism showing the changes according to the maturation of the neuronal systems. Whether later symptoms are primary or secondary remained unanswered. So the initial symptoms occurring in infancy and early childhood were correlated to later symptoms of dysfunction of the higher cortical function, which is assessed by the ability to speak words.

Ages at which motor milestones were attained and those at onset of seizures and stereotypy were correlated between the groups with and without words. A correlation was observed in locomotion (ie, crawling and gait).[26] The same analysis was done with an increased number of patients (n = 100, 60 with words and 40 without). The results were the same, although the P values differed (ie, the significant differences were observed in crawling [P = .0068] and walking [P = .0533]). The rest of the motor milestones and the onsets of the stereotypy and seizures did not differ between the groups with and without words (Figure 1).

When the grade of stagnation of the head circumference was correlated to developmental failure among four groups (ie, words [+] gait [+], words [+] gait [−], words [−] gait [+], and words [−] gait [−]), it was revealed that stagnation was most prominent in the group of words (−) gait (−).[26] It was also shown that the stereotyped movement correlated to the regression of higher cortical function.[26]

SUMMARY OF SLEEP STUDIES

Sleep is a physiologic behavior controlled by the aminergic neurons in the brain stem and the midbrain and the cholinergic neurons of the pons. Sleep-wake rhythm can be analyzed by reviewing a sleep diary, and sleep parameters are measurable by polysomnography.[27] To identify the involvement of the aminergic neurons of the brain stem and the midbrain in Rett syndrome, we evaluated the sleep-wake rhythm and polysomnography in patients.

In infancy, patients with Rett syndrome tended to sleep longer during the day, with a delay in the formation of day-night rhythm. As these patients grew older, there was a delay in physiologic decline in daytime sleep and total daytime sleep time was longer compared with that of normal peers. The lack of decrement of the daytime sleep observed in Rett syndrome indicates development of abnormal sleep amplitude after 4 months of age.[4,14] However, circadian sleep-wake rhythm developed.

The results of polysomnography revealed that rapid eye movement (REM) sleep parameters are present by 36 weeks' gestational age.[8,9,28,29] Abnormalities included the development of the phasic inhibition index,[30] that is, inhibition of the twitch movement appearing in the period of burst occurrence of REMs in REM stage and leakage of atonia of REM stage into non-REM, which indicate that the abnormality is taking place between 36 or 38 weeks' gestational age and 4 months' postnatal age and suggest hypofunction of noradrenergic and 5-hydroxytryptamine neurons. Body movements during sleep were studied. Both gross movements and twitch movements revealed

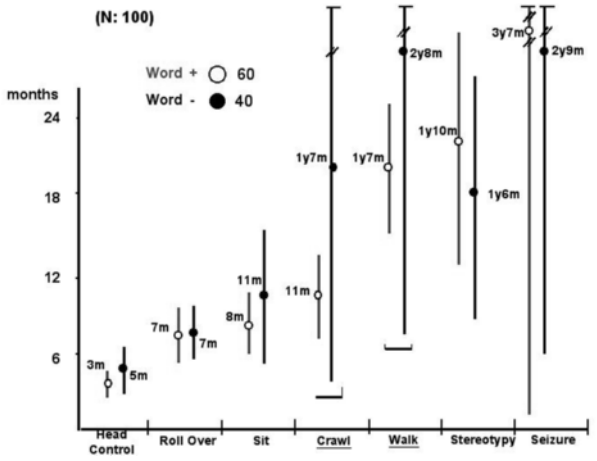

Figure 1. Differences of the ages at which motor milestones were attained and onset of stereotypy and seizures in the patient groups with or without words.

different patterns between patients younger than 6 years of age and older than that.[12] Frequencies of twitch movements in REM stage in younger children showed a decrement, suggesting hypofunction of dopaminergic transmission, but older patients showed an increment, suggesting an increase in dopaminergic transmission owing to the occurrence of supersensitivity of dopaminergic receptors.

PATHOPHYSIOLOGY

The natural course of Rett syndrome is unique. The age-dependent appearance of the specific clinical features reflects the changes occurring along the maturation of the responsible neuron or neuronal systems. The age-dependent feature of the disorder is important when considering the pathophysiology. During the maturation of the nervous system, it is important to remember that the responsible neurons or neuronal systems have to reach certain levels of maturation for symptoms to manifest.[8,31]

The earliest clinical features of Rett syndrome are hypofunction of postural tone and failure in locomotion, which are caused by hypofunction of the brainstem aminergic neurons (ie, noradrenergic and 5-hydroxytryptamine neurons). These cause a poor response to environmental stimulation, poor formation of circadian rhythm, and more sleeping during daytime, which also induces autistic tendency.

Characteristic stereotyped hand movement appears after loss of purposeful hand use. This movement is also characterized by the fixed position of the hand, which does not change through the course. Furthermore, the hand or fingers show dystonic posture. We can replicate the pattern in a monkey with a lesion in the unilateral supplementary motor area.

Thus, dysfunction of the substantia nigra–dopaminergic neuron causes dystonic hypertonus through the descending pathway of the basal ganglia and suppresses purposeful hand use and stereotyped movements by inducing dysfunction of the premotor area and the supplemental motor area through the basal ganglia–thalamo-cortical pathways. As mentioned before for the repetitive stereotyped movement, the occurrence of dopaminergic receptor supersensitivity might be involved.

Age-dependent clinical features are observed in the changes of the hand stereotypy. It initially starts as the normal behavior of the hand clapping, particularly when the child gets excited. As these children age, the dystonic posture begins to develop and the characteristic hand stereotypy of Rett syndrome appears.

We suggested that dysfunction of higher cortical function correlates with the grade of deceleration of head growth and grade of severity of failure of locomotion but not with stereotyped movements. These suggest that the locomotion is the key function reflecting development of higher cortical function, here evaluated by the ability to speak words. Which neuronal system underlies this?

Locomotion is under the control of the propriospinal locomotion systems, and for this system to activate, tonic innervation of the brainstem noradrenergic and 5-hydroxytryptamine neurons is necessary through the descending reticulospinal projection from brainstem noradrenergic and 5-hydroxytryptamine systems.[32]

Analysis of the sleep studies also suggested that the behavior in the early infancy is due to the hypofunction of the 5-hydroxytryptamine and noradrenergic system in the brain stem and that in late infancy to early childhood, dopaminergic dysfunction leads to the characteristic symptoms. Restriction of atonia in REM stage from 4 months of age induces synaptogenesis of the brain and makes possible integrative function of the brain. Thus, the existence of atonia in non-REM stages after 4 months causes failure to develop controlled and integrated activity of the whole brain. Furthermore, noradrenergic dysfunction in this period causes profound failure of the synaptogenesis of the cortex, except the occipital area, and causes microcephalus.[4,8,9,31] Leakage of atonia of REM stage into non-REM sleep also causes inhibition of all reflex systems, including those of the autonomic nervous system. This can later appear as abnormal respiration.

The brain-stem monoaminergic system involved in postural tone and locomotion can influence the function of the pedunculopontine tegmental nucleus. Dysfunction of these aminergic neurons causes dysfunction of the pedunculopontine tegmental nucleus and consequently induces dysfunction of the nigrostriatal and the ventrotegmental dopaminergic neurons and the Meynert nucleus. The dysfunction of these nucleus could finally cause the failure of the synaptogenesis of the frontal cortex directly or through the basal ganglia and cause marked failure in synapses and dendrite formation of the frontal cortex. These processes appear in the neuropathologic and neurohistochemical findings of Rett syndrome. Neuropathology shows a brain the size of a normal 12-month-old child without degenerative changes[33] but reduced size of neurons in the frontal cortex and reduced dendritic branching of pyramidal neurons of frontal, temporal, and motor cortices in layers III and V, with predominance in the frontal cortex. These suggest a developmental failure.

Alterations in neurochemical substances showed that the abnormality involved the 5-hydroxytrypamine, dopamine, substance P, choline acetyltransferase, microtubule-associated proteins 2 and 5, cyclooxgenase 2, adenosine monophosphate acid, and *N*-methyl-D-aspartate receptors (NMDA), nerve growth factor and glutamate (cerebrospinal fluid). These biochemical changes suggest the involvement of neuronal processes for the structural changes.

An excitotoxic lesion of the pedunculopontine tegmental nucleus produced contralateral hemiparkinsonism in a monkey, which caused decreased tyrosine hydroxylase in the substantia nigra without gliosis.[34] These are identical to the changes in the substantia nigra seen in Rett syndrome. These suggest that dysfunction of 5-hydroxytryptamine and noradrenaline neurons causes dopaminergic dysfunction via the pedunculopontine tegmental nucleus.[34] Animal studies suggested the involvement of the dopaminergic neuron for stereotypy in an methyl-phenyl-tetrahydropyridine-treated monkey, in that dopaminergic lesion of striatum with dopaminergic receptor supersensitivity (Hikosaka and colleagues, personal communication). These experiments postulate the neuronal processes underlying how the early hypofunction of 5-hydroxytryptamine and noradrenergic neurons causes hypofunction of dopaminergic neurons and the involvement of dopaminergic receptor supersensitivity leading to repetitive stereotyped movements. The correlation of the clinical severity to a certain mutation pattern of the causative gene, methyl-CpG binding protein 2 (*MECP2*), is shown in some cases. However, the exact role of *MECP2* in the early process, particularly for the aminergic neurons, has not yet been clarified. Further research on the clinicobiologic correlation will contribute to the understanding of the natural course of the disorder.

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Original Article

Does Genotype Predict Phenotype in Rett Syndrome?

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ABSTRACT

Mutations in the X-linked gene encoding the methyl-CpG binding protein MeCP2 are the primary cause of classic and atypical Rett syndrome and have recently been shown to contribute to other neurodevelopmental disorders of varying severity. To determine whether there are molecular correlates to the phenotypic heterogeneity, numerous groups have performed genotype-phenotype correlation studies. These studies have yielded conflicting results, in part because they used different criteria for determining severity and classifying mutations. Evolution of the phenotype with age and variable expressivity arising from individual variability in X-chromosome inactivation patterns are among other reasons the findings varied. Nonetheless, evidence of differences in the phenotypic consequences of specific types of mutations is emerging. This review analyzes the available literature and makes recommendations for future studies. (*J Child Neurol* 2005;20:768–778).