

RETT's Syndrome in Korea - Report of Two Cases -

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Rett's syndrome(RS) is a progressive neurodegenerative disorder characterized by exclusive occurrence in females, autistic behavior, dementia, gait ataxia, loss of purposeful use of the hands with stereotypic hand movement, and seizures. Initially RS was considered to be very rare ; however, recent reports suggest that the prevalence is considerably higher and occurrence is world-wide. Because the pathophysiological process remains unknown, the diagnosis of RS is based mainly on its characteristic clinical features and course. We experienced two cases of RS which, to our knowledge, are the first reported in Korea. It is quite possible that many patients with RS are not yet being diagnosed in Korea.

Key Words : Rett's syndrome, haloperidol

Rett's syndrome is a progressive disorder characterized by regression of language and motor development, stereotypic hand movement, autistic behavior, seizures, episodic hyperventilation/apnea, bruxism, gait ataxia, and acquired microcephaly (Hagberg et al. 1983). It was initially described by Andreas Rett in 1966; however, only recently has this disorder been reported world-wide including Europe, U.S.A. and Japan.

Although it has been suggested that RS is due to an X-linked dominant mutation(Coming 1986), the pathogenesis of RS remains unknown. There are no confirmatory laboratory tests for this disorder. and the diagnosis is primarily based on the clinical criteria(Hagberg et al. 1986; Rett Syndrome Diagnostic Criteria Work Group, 1988). To our knowledge, RS had not been reported to occur in Korea. We report on two cases of RS with a brief review of the literature.

PATIENTS' REPORT

Patient 1

A 5 year 7 month old girl presented with frequent episodes of hyperventilation/apnea, seizures, and delayed development. She had a normal gestation and birth. She was noted to have congenital blepharoptosis. Her development had been normal until she was one year old. She failed to walk by 18 months. At the age of 18 month, she was admitted to the hospital because of seizures with high fever.

Thereafter, she has been having one or two episodes of generalized convulsion per month. At the age of 2, a resection of levator muscle(OU) was done to correct congenital blepharoptosis. Extensive diagnostic evaluation including chromosomal study was conducted with negative results. At the age of 5, she began to show recurrent episodes of hyperventilation and apnea while awake. The episodes sometimes lasted longer than one to two minutes, resulting in cyanosis and loss of consciousness. Abnormal respiration disappeared completely during sleep. In addition, she showed ataxic gait and regression of language skill and diminished hand usage with stereotypic washing or rubbing movement of hands. On examination, head circum-

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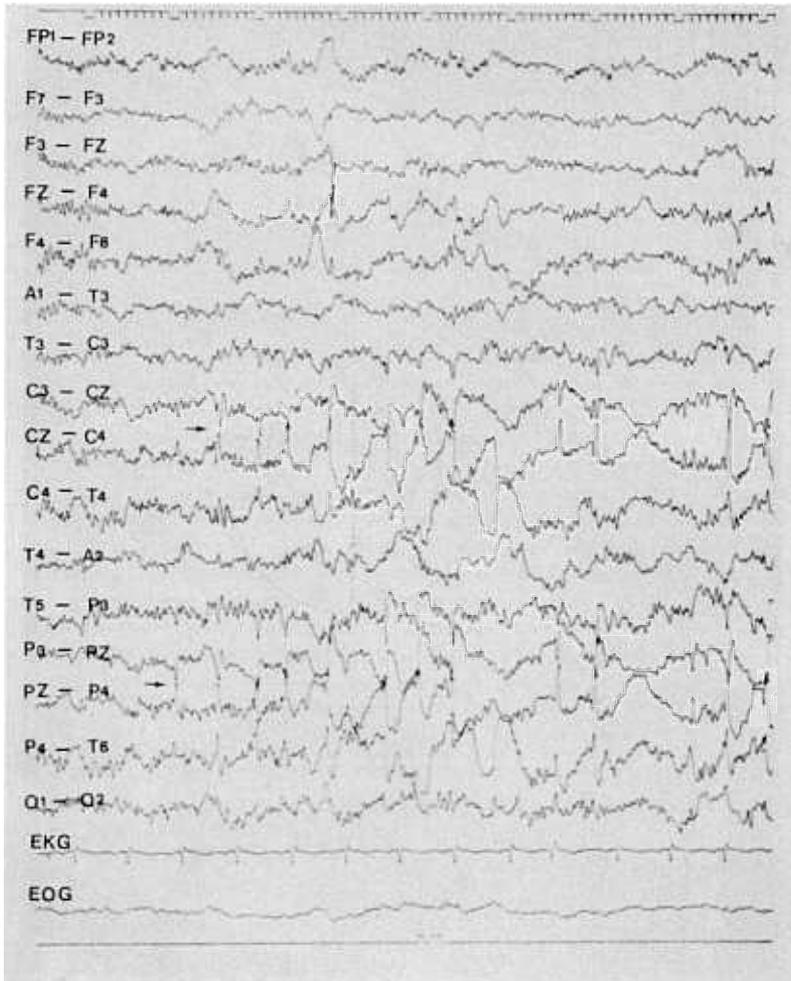


Fig. 1. EEG from patient 1 showing epileptiform discharges in the midline parietal area.

ference was less than 3 percentile, but height was in the range of 75-90 percentile, weight 25-50 percentile.

Cranial nerve examination was normal. Deep tendon reflexes in lower extremities were symmetric but increased with unsustained ankle clonus bilaterally. Denver developmental screening test demonstrated personal-social function of 12 months; language, 11 months; fine motor, 22 month; gross motor, 21 months. Laboratory studies showed normal CBC, ESR, serum electrolyte, and liver function test. Serum NH_3 and ceruloplasmin were normal. Thyroid function test, vitamin B12, folate, and serum amino acid assay were within normal range.

Electrocardiogram and evoked potential studies (VEP, BAEP, SEP) were also normal. EEG showed interictal epileptiform discharges in midline parietal area with diffuse slowing of background rhythm (Fig. 1). Brain CT scan and MRI were normal (Fig. 2A). CCTV-EEG monitoring captured recurrent episodes of hyperventilation/apnea occurring at the frequency of nearly one every 10 minutes. Those were not associated with any electrographic seizure activity, but accentuated background slowing at the end of apnea probably due to hypoxia. Haloperidol 1.5 mg/day in three divided doses was started with a profound reduction of episodes of hyperventilation/apnea and some improvement of the stereotypic

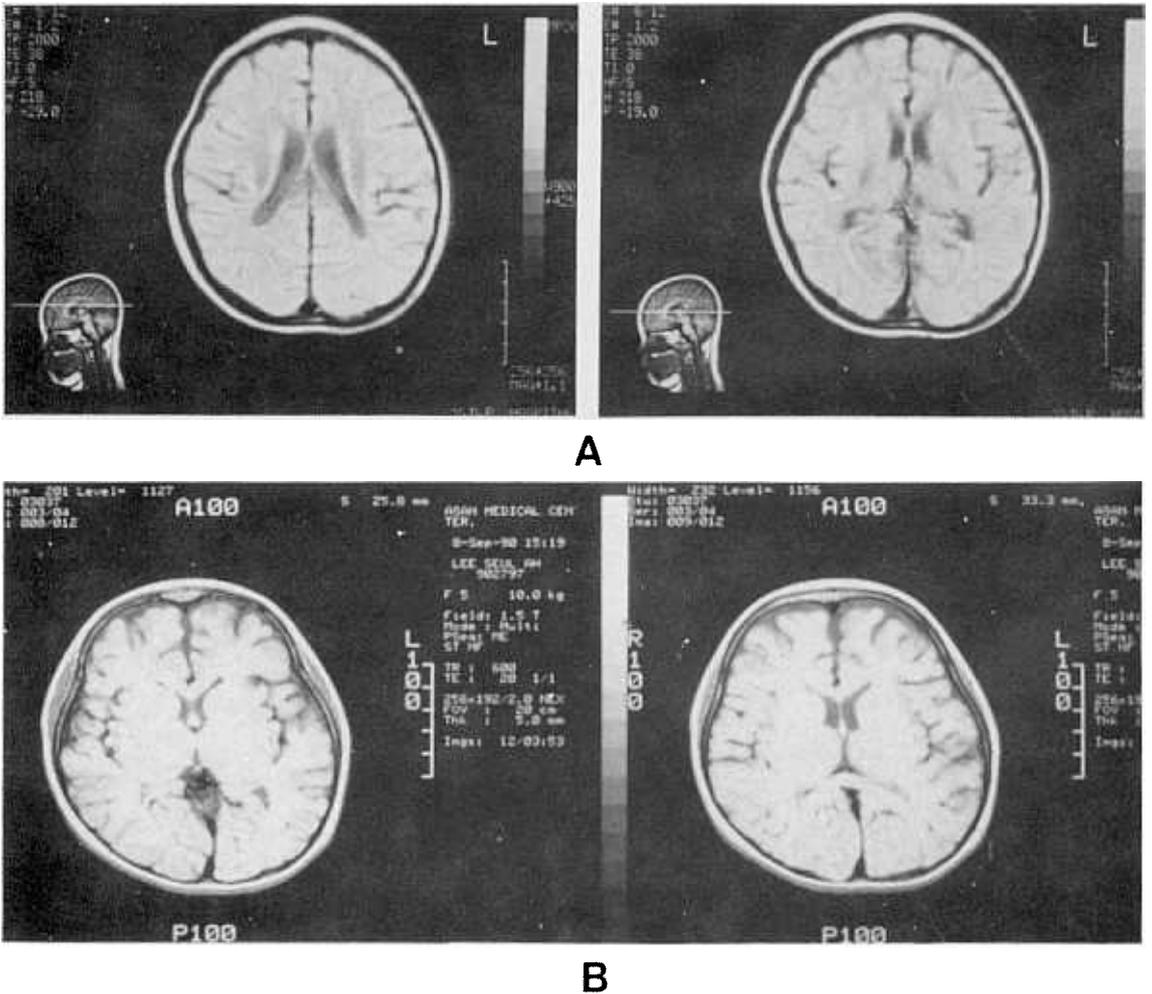


Fig. 2. MRI of brain : (A) patient 1(TR 2000, TE 38) showing normal, (B) patient 2(TR 600, TE 38) showing mild cortical atrophy.

hand movement. Subsequent discontinuation of haloperidol for one week brought the frequency of hyperventilation back to the baseline level(every 10 minutes). Prompt restoration following readministration of the drug confirmed the definite therapeutic effect of haloperidol.

Patient 2

A 5 year-old girl presented with growth and developmental delay with respiratory irregularities (hyperventilation and apnea). Her gestation and birth were normal. She rolled at 4 months, crept at 6 months, sat alone at 9 months but was unable to achieve further milestones. She was able to speak

two words at 12 month of age but became unable to speak by 18 month. She began to show autistic behavior(poor eye contact and loss of interest to external environment), stereotypic hand movement such as hand mouthing, rubbing and tapping. At the age of 3 years, recurrent episodes of hyperventilation/apnea as well as prominent bruxism developed. She began to exhibit increased muscle tone with muscle wasting at age of 4 year. On examination, her head circumference was below 3 percentile, height at the 25 percentile, weight below 3 percentile. She was profoundly retarded with inability to speak and lack of purposeful hand use, although she showed frequent hand move-



Fig. 3. Patient 2 showing characteristic stereotypic hand movement with mouthing and tapping.

ment with mouthing, rubbing, and tapping(Fig. 3). There were no signs of retinopathy or cranial nerve abnormalities. Severe diffuse muscle wasting was noted.

Developmental assessment using Denver developmental screening test demonstrated personal-social function at 9 months; language, 10 months; fine motor, 4 months; gross motor, 10 months. The following laboratory studies were within normal limit : CBC, ESR, serum electrolyte, liver function test, serum NH₃, thyroid function test, chromosomal study(46XX), serum amino acid assay, EKG, NCV&EMG, and sensory evoked potentials(VEP, BAEP, SEP). EEG showed focal interictal epileptiform discharges in the left central and the right parietal areas with diffuse background slowing(Fig. 4). Brain CT scan and MRI showed mild cortical atrophy(Fig. 2B). Polysomnographic study demonstrated decreased duration of REM sleep(Table 1). Recurrent episodes of hyperventilation/apnea were found only during the waking state(Fig. 6). Haloperidol(1.5

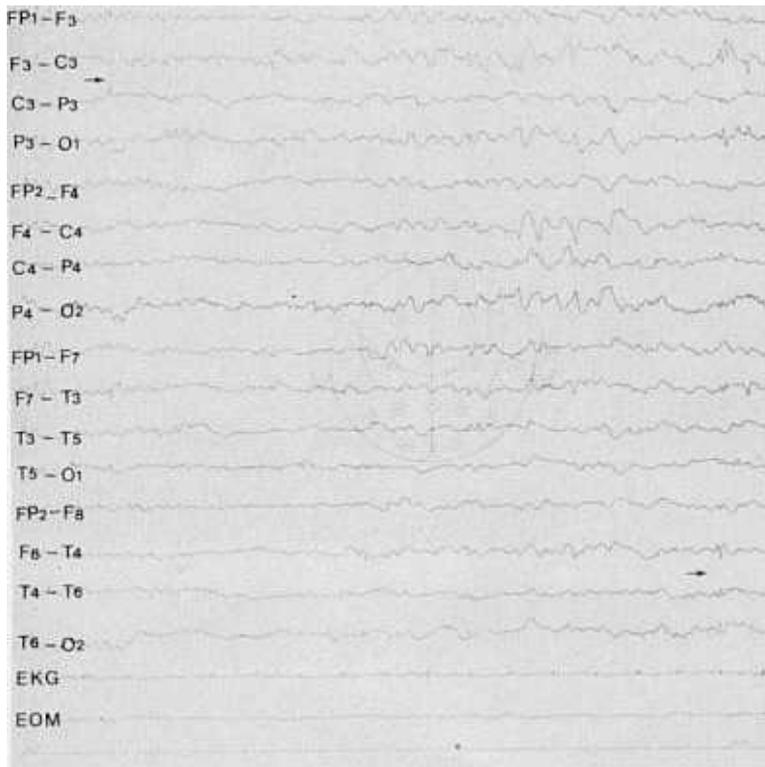


Fig. 4. EEG from patient 2 showing epileptiform discharges in the left central and the right parietal area with diffuse background slowing.

mg/day) was started without apparent benefit in this patient.

DISCUSSION

RS was first described by Andreas Rett in 1966 as

a progressive disease named "cerebral atrophy associated with hyperammonemia" (Rett 1966, 1977). But this report did not received much attention until the 1980's when many new cases were found in Europe, U.S.A. and Japan (Hagberg 1983; Moeschler *et al* 1988; Nomura 1984).

The prevalence of RS was as high as 0.65/10,000 female children aged 6 to 17 in Sweden(Hagberg 1985). In England, it was estimated as 0.80/10,000 in female children aged under than 14 year(Kerr AN, 1986). A study from Japan reported a some what lower prevalence of 0.36/10,000 female children(Fujino and Hashimoto 1989).

Pateints with RS do not have a specific family history. Their birth is usually normal without recognizable complications during perinatal period. They develop normally until 6-18 months after birth, when gradual cessation and regression of development appears. Loss of language skill and autistic behaviors may appear in the early stage.

Shortly after, a psychomotor regression becomes prominent with a gradual disappearance of autism. During late infancy or childhood(1-4 years old), characteristic stereotypic hand movement(wringing,

Table 1. Polysomnographic findings in patient 2

Polysomnographic Findings	
Bed Time	: 600 min. (9 pm. - 7 am.)
Sleep Time	: 302 min.
Wake Time	: 298 min. Sleep Efficiency : 50%
Sleep Stage I	: 25% (2 - 5%)
Stage II	: 60% (45 - 55%)
Stage III/IV	: 15% (3 - 8%)
REM	: 1 min. (<1%) (20 - 25%)
Total Apneic Episodes	: 230/10 hr.
Apneic Index	: 23 (NL. <5)
Awake	: 42 (210/298 min./60 min.)
Sleep	: 4 (20/302 min./60 min.)



Fig. 5. Polysomnography from patient 2 showing hyperventilation and apnea in awake state.

clapping, tapping, rubbing, mouthing), ataxic gait, and episodes of hyperventilation/apnea appear. Seizures occur in 75% of the patients. Later, increased muscle tone, muscle wasting, bruxism, constipation, and scoliosis may become gradually prominent.

A recently introduced clinical staging system provides a valuable guideline for the diagnosis and identification of the natural history (Hagberg et al. 1985); Stage I, the 'stagnation stage' is characterized by a developmental arrest with hypotonia in the period of 6 to 18 months. Stage II, the 'rapid destructive stage', begins by the age of 1-4 years and is characterized by the appearance of stereotypic hand movements with loss of acquired hand skills, irregular breathing (hyperventilation and apnea) and seizures. Stage III, the 'pseudostationary stage', beginning at age 4-8 years, is characterized by gait disturbances, mental retardation and seizures. Stage IV, the 'late motor deterioration stage', appears in adolescence to be characterized by progressive motor disturbances resulting in scoliosis, muscle wasting and bed-bound state.

Although a few cases of family history have been reported (Hanefeld 1985; Hagberg 1983), most RS occur sporadically. Because it is found only in girls, X-linked dominant mutation was proposed (Comings 1986).

Neuropathologic features of RS are rather nonspecific: microcephaly with decreased brain weight, diffused cortical atrophy increased neuronal lipofuscin with mild gliosis, and underpigmentation of the zona compacta nigrae (Jellinger et al. 1988).

In a few cases, neurotransmitter assays in RS demonstrated increased β -endorphin in the thalamus and cerebellum, increased level of dopamine, norepinephrine, homovanillic acid in the CSF. Myer et al. (1988) also reported a normalization of β -endorphin by administration of naltrexone, an opioid antagonist. These findings may suggest that altered regulation of neurotransmitters play a role in the pathogenesis of this disease. However, it is not clear whether these are primary or secondary changes. Additionally, Perry et al. (1988) asserted no alteration of neurotransmitters metabolism in RS.

EEG findings in the early period may be normal, but after age of 3, slowing of background activity along with focal epileptiform discharge begins. The epileptiform discharges mainly locate around the middle third of the head, accentuated during light sleep (Verma et al. 1986, Glaze et al. 1987, Robb 1989). The EEG findings seem quite useful but do not provide confirmatory clues for the diagnosis

(Robb 1989).

Polysomnographic studies shows that the REM sleep is reduced and stage 2 sleep is increased. The episodes of hyperventilation/apnea is usually significantly reduced during sleep (Glaze et al. 1987), as was in our case.

Treatment is symptomatic and supportive. There is no specific treatment reported yet. The seizures usually respond well to conventional antiepileptic treatment. Naltrexone (Myer 1988) or ketogenic diet (Haas et al. 1985) has been reported to be effective in some cases, but not yet confirmed (Myer 1988). Interestingly, administration of haloperidol was associated with significant reduction of episodes of hyperventilation/apnea in the first case but not the second case. The therapeutic role of haloperidol has not been reported in current literature, thus requiring further investigation.

The entity of RS is certainly a diagnostic category based on the clinical criteria (Hagberg et al. 1985, The Syndrome Diagnostic Work Group 1988), which differentiates it from other congenital and degenerative diseases in childhood. Our cases were diagnosed by diagnostic criteria, but also were differentiated from other congenital or metabolic diseases through exhaustive laboratory tests including brain imaging studies.

We suspect sure that there are many RS cases existing in Korea. Our two cases were previously diagnosed as cerebral palsy before coming to our attention. The recognition of this entity would provides definite prognostic and therapeutic perspectives to the family as well as physicians. Therefore, the possibility of RS should be to be considered during the evaluation and management of unexplained childhood psychomotor retardation.

REFERENCE

- Cirignotta F, Lugaesi E, Montagna P: Breathing impairment in Rett syndrome. *Am J Med genet* 24: 167-173, 1986
- Glaze DG, Frost JD, Zoghbi HY, Percy AK: Rett's syndrome: Characterization of respiratory patterns and sleep. *Ann Neurol* 21: 377-382, 1987
- Glaze DG, Frost JD, Zoghi HY, Percy AK: Rett's syndrome: Correlation of electroencephalographic characteristics. *Arch Neurol* 44: 1053-1056, 1987
- Haas RH, Rice MA: Is Rett's syndrome a disorder of Carbohydrate metabolism? Hyperpyruvicacidemia and treatment by ketogenic diet. *Ann Neurol* 18: 418, 1985
- Hagberg B, Aicardi J, Dias K, Romos O: A progressive

- syndrome of autism, demntia, ataxia, and loss of purposeful hand use in girls : Rett's syndrome : report of 35 cases. *Ann Neurol* 14 : 471-479, 1983
- Hagberg B : Rett's syndrome : Prevalence and impact on pregressive sever mental retardation in girls. *Acta Pediatr Scand* 74 : 405-408, 1985
- Hagbert B, Goutieres F, Hanefield F, Rett A, Wilson J : Rett syndrome : Criteria for inclusion and exclusion. *Brain Dev* 7 : 372-373, 1987
- Hagne I, Witt-Engerstrom I, Hagberg B : EEG development in Rett syndrome. A study of 30 cases. *Electroencephalogr. Clin Neurophysiol* 72 : 1-6, 1989
- Hasekawa M, Momura Y, Sekawa M : Rett syndrome : Clinical studies. *No To Hattatsu* 18 : 269-279, 1986
- Jellinger K, Armstrng D, Zoghbi HY, Percy AK.: Neuropathology of Rett syndrome. *Acta Neuropathol* 76 : 142-158, 1988
- Kerr AM, Stephenson JBP : Rett syndrome in the West Scotland. *Br Med J* 291 : 579-582, 1985
- Moeschler JB, Charman DE, Berg SZ, Graham JM : Rett syndrome : Natural history and management. *Pediatr* 82 : 1-10, 1988
- Myer EC, Morris DL, Brase DA, Dewey WL : Hypereendorphinism in Rett syndrome : Case or Result? *Ann Neurol* 24 : 340-341, 1988
- Nomura Y, Segawa M, Hasegawa M : Rett syndrome-clinical studies and pathophysiological consideration *Brain Dev* 6 : 475-486, 1984.
- Olsson B, Rett A : Autism and Rett syndrome : Behavioral investigation and differential diagnosis. *Developmental Med and Child Neurol* 29 : 429-441, 1987
- Perry TL, Dunn HG, Ho HH, Crichton JU : Cerebral fluid values for monoamine metabolites, gamma-aminobutyric acid, and other amino compounds in Rett syndrome. *J Pediatr* 112 : 234-238, 1988
- Rett A : *Cerebral atrophy associatioed with hyperamonemia*, in Vinken PJ, Bruyn GW(eds) : *Handbook of Clinical Neurology*. New York, North-Holland Publishing Co. vol 29, 1977, 305-329
- Robb SA, Harden A, Boyd SG : Rett syndrome : An EEG study in 52 girls. *Neuropediatr* 20 : 192-195, 1989
- Robertson R, Langill L, Wong PKH : Rett's syndrome : EEG presentation in six cases. *Electroencephalogr Clin Neurophysiol* 64 : 79, 1986
- The Rett Syndrome Diagnostic Criteria Work Group : Diagnostic Criteria for Rett syndrome. *Ann Neurol* 23 : 425-428, 1988
- Thomas S, Hielm M, Oberholzer V, Brett Em, Wilson J : Rett syndrome and ornithinine carbamoyltransferase deficiency. *Lancet* 5 : 1330-1331, 1987.
- Trauner DA, Haas RH : Electroencephalographic abnormalities in Rett syndrome. *Pediatr Neurol* 3 : 331-334, 1987
- Trauner DA, Haas RH : Electroencephalographic Abnormalities in Rett's syndrome. *Ann Neurol* 18 : 394, 1985
- Verma NP, Chheda RL, Nigro MA, Hart ZH : Electroencephalographic finding in Rett syndrome. *Electroencephalogr. Clin Neurophysiol* 64 : 394-401, 1986
- Witt-Engerrstrom I, Gillberg C : Rett syndrome in Sweden. *J Autism Del Dis* 17 : 149-150, 1987
- Zoghbi HY, Percy AK, Glaze DG, et al : Reduction of biogenic amine levels in the Ret syndrome. *N Engl J Med* 313 : 921-924, 1985