The Japanese Journal of Psychiatry
and Neurology, Vol. 45, No. 2, 1991

Roles of a Subependymal Nodule of Tuberous Sclerosis on Pathophysiology of Epilepsy

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Abstract: Polysomnographies (PSG) were performed on two cases with tuberous sclerosis (TS), both having subependymal nodules on the medial wall of the caudate nucleus adjacent to the thalamostriatal sulci. Clinically one had suffered from infantile spasm and which later turned out to be complex partial seizure with a rotation toward the right. The other had developed tonic seizure on the right with a rotation toward the left in early childhood. Clinico-pharmacological studies revealed the existence of synaptic supersensitivity of the dopamine (DA) receptor in the left caudate and PSG confirmed the synaptic supersensitivity of the former, while in the latter case, it suggested a decrease in DA activity on the left. Subependymal nodules in the caudate nucleus could cause a reduction in the DA transmission and develops synaptic supersensitivity after suffering from TS.

Key Words: *tuberous sclerosis, infantile spasm, rotatory seizure, subependymal nodule, polysomnography, dopaminergic postsynaptic supersensitivity*

Jpn J Psychiatr Neurol 45: 372–377, 1991

INTRODUCTION

From PSG examinations on cases with TS combined with epileptic seizure, we have already shown that subependymal nodules located on the head of the caudate nucleus at the anterior horn of the lateral ventricle modifies the function of the nigrostriatal (NS) dopaminergic neurons[1] and that, in cases who had suffered from infantile spasms, synaptic supersensitivity of the DA receptor, caused by the blocking of the DA transmission by the ependymal nodule, has a role in the pathophysiology of infantile spasms. In this study we correlated a case of infantile spasm with that of partial seizure having nodules on the same locus, and re-evaluated the effects of the nodules in the pathophysiology of epilepsy.

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SUBJECTS AND METHODS

Case R.K. was an 18-year-old woman with tuberous sclerosis who suffered from infantile spasm in infancy and later suffered from clockwise rotatory seizure since childhood. Her attacks consisted of a clockwise rotation of one and one half times or more followed by forward rushing and by meaningless smile and moaning. A brain CT scan revealed a tubercle located in the anterior horn of the left ventricle (Fig. 1). These

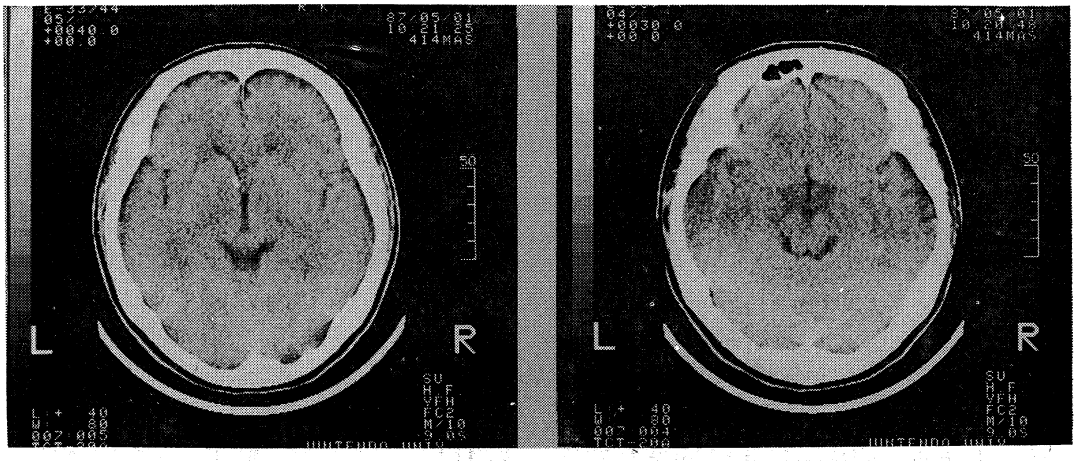

Fig. 1: CT scans of Case R.K. showing a tubercle located in the anterior of the ventricle.

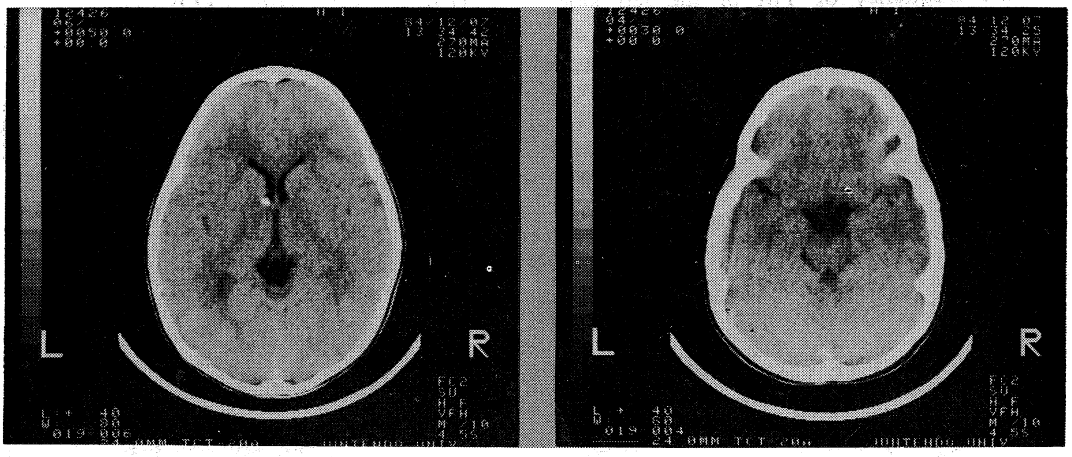

Fig. 2: CT scans of Case T.E. showing a tubercle located in the same region as Case R.K.

rotatory seizures were aggravated by small doses of L-dopa (100 mg per day) and alleviated by pimozide. This clinical and pharmacological situation was considered to be due to postsynaptic supersensitivity occurring in the left striatum.[1]

Case T.E. was an 8-year-old boy with tuberous sclerosis whose tubercle was located in the same region as Case R.K. (Fig. 2). He fell down from a baby bed at the age of 20 months and developed focal tonic seizure located in his right arm after 3 days. He suffered from other focal seizures which consisted of a counter-clockwise rotation followed by tonic seizure of his right arm.

Polysomnography was performed with the Segawa[2] method. We evaluated two types of body movements; gross movements (GM)-diffuse sequential muscle activities including those of the rectus abdominalis, lasting more than 2 seconds and twitch movements (TM)-short muscle activities located on one

muscle, lasting less than 0.5 second. The number of each body movement (BM) against one hour of each sleep stage (rate of BMs) was estimated, and the mode of occurrence of BMs against sleep stages were evaluated.

RESULTS (Figs. 3, 4 and 5)

Case R.K.: Before treatment, the frequency of GM in stage REM was markedly reduced compared to normal values while the rates of other sleep stages remained in the normal range. The frequency of bilateral TM had obviously increased in all the sleep stages, while the pattern of occurrence was normal. After L-dopa (4 mg/kg/day), the abnormalities about GM were aggravated but the frequency of TM of the left side had decreased with a slight exaggeration on the right. And clinically rotatory seizure worsened. After a very small dose of L-dopa (0.5 mg/kg/day), the abnormalities of PSG became normalized with clinical improvement.

Case T.M.: Before treatment, the frequency of GM was increased and that of TM was slightly decreased on the right side less than the left side.

DISCUSSION

Clinical and pharmacological characteristics of case R.K. suggested the existence of

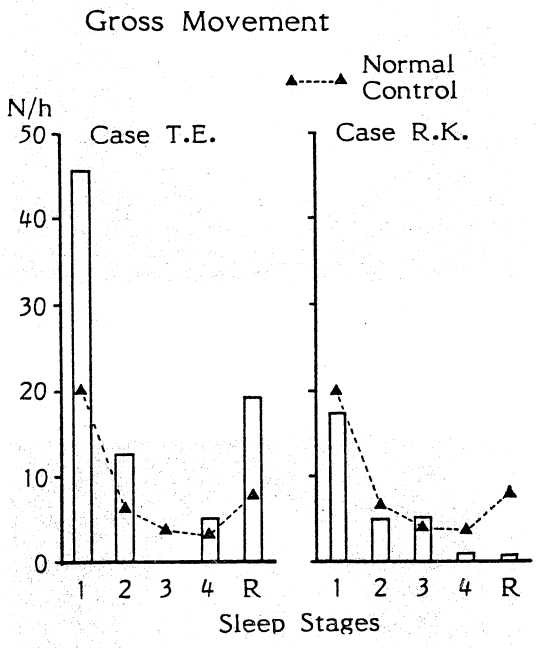

Fig. 3: Gross movements in each case. Abscissa—sleep stages (1–4: stage 1–4, R: stage REM), ordinate—N/h: number of GM per hour of each stage.

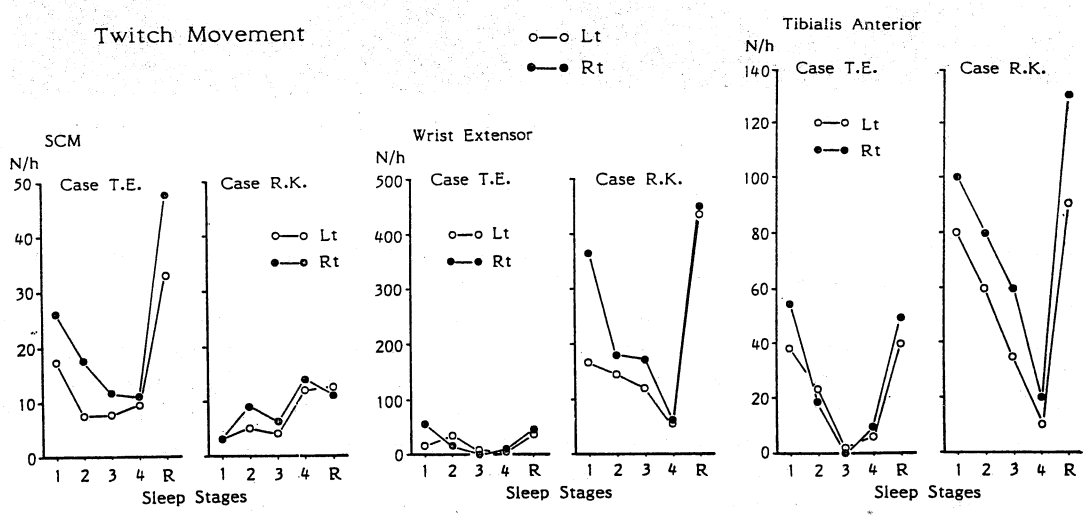

Fig. 4: Twitch movements in each case. The values of TM shown in the three different muscles. SCM: sternocleidomastoideus.

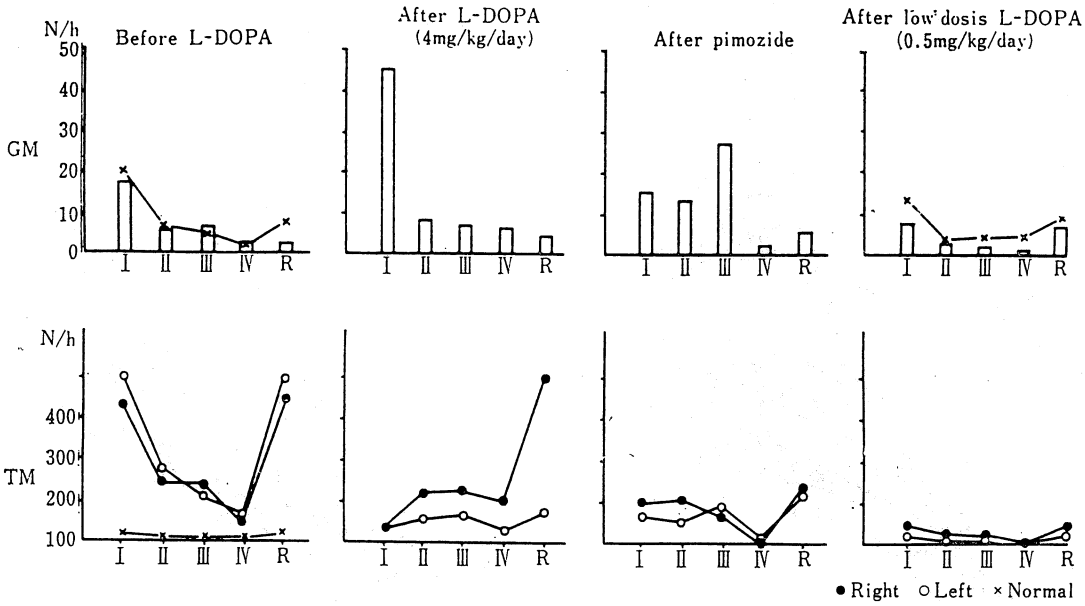

Fig. 5: Gross movements and twitch movements in the wrist extensor of Case R.K. Modulation of the rate of occurrence against each sleep stage before and after each treatment.

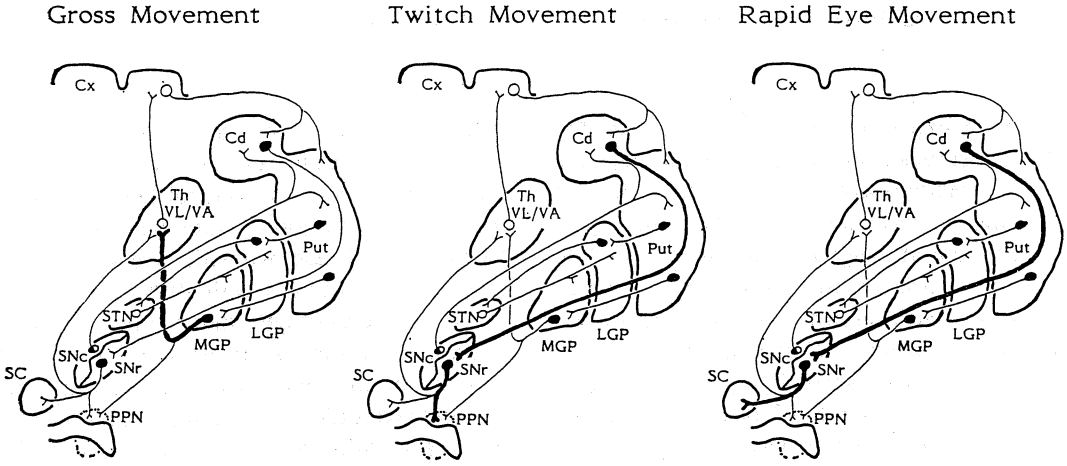

Fig. 6: The scheme of the neural systems of each movement during sleep. Left: GM controlled by the pallido-thalamic pathway to cerebral cortex; middle: TM controlled by the striatofugal pathway to PPN; right: rapid eye movements controlled by the striatofugal pathway to superior colliculus.

synaptic supersensitivity of the nigrostriatal DA neuron at the left caudate nucleus. This implicates the decrease in DA release at the neuron which might be caused by the subependymal nodule. If so, the ipsilateral rotation toward the nodule observed in case T.M.

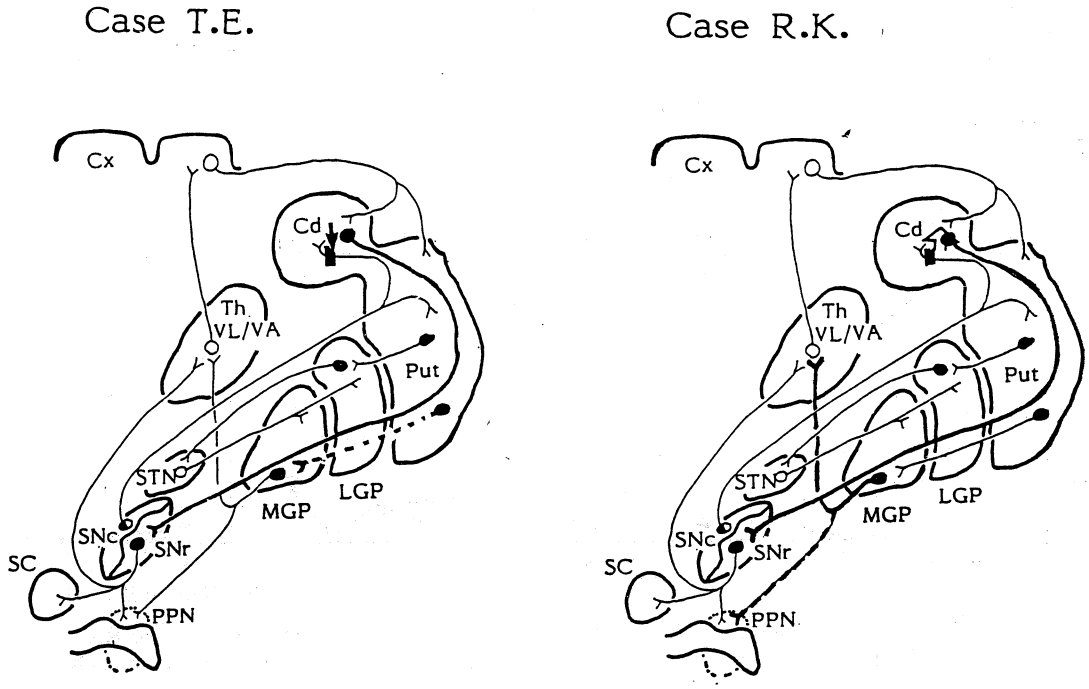

Fig. 7: Right: the scheme of synaptic supersensitivity of the nigrostriatal DA neurons at the left caudate nucleus in Case R.K.; left: the scheme of the decreased pattern of the nigrostriatal DA neurons at the left caudate nucleus in Case T.E.

could be explained by the decrease in the DA transmission at the left caudate nucleus.

The caudalofugal pathway for rotatory movements has not been clarified. However, the basal ganglia is known to modulate the locomotion in the striatofugal pathway to the pedunclo-pontine nucleus (PPN) via the pars reticulata of the substantia nigra (SNr).[5] From polysomnographical examinations of various kinds of basal ganglia diseases, we showed that TMs during sleep is controlled by the striatofugal pathway to PPN or the reticulospinal tract (Fig. 6).[4] As there was a correlation between the features of TMs and rotatory movements, the rotatory seizure observed in these cases might be modulated by the pathway, caudate nucleus-SNr-PPN (Fig. 7).

There are two descending pathways from the midbrain which controls locomotion and posture. One through the ventral tegmental field exaggerates the tone of antigravity muscles and facilitates locomotion and the other via the dorsal tegmental field depresses the tone of antigravity muscles and ceases locomotion.[3] These two pathways are thought to have a connection with PPN.[5]

The caudalo-fugal descending impulse, generated by the supersensitized DA receptors on the nucleus, causes generalized tonic or atonic condition, by stimulating the ventral or dorsal pathway. These pathophysiologies might relate to tonic salaam spasms of infantile spasms and tonic or astatic drop attack of Lennox syndrome, respectively.

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