Menkes Kinky Hair Disease Presenting with Pseudoperiodic Tonic Spasms during the Clinical Course

Shinichi YAGI, Naoki KATAOKA, Yo MIURA, Shun MIZUTA and Tetsuro MORITA

Department of Pediatrics, Kawasaki Medical School, Kurashiki 701-01, Japan

Accepted for publication on December 18, 1991

ABSTRACT. A case of Menkes kinky hair disease presenting with pseudoperiodic tonic spasms during the clinical course is described. The reported case had been treated by parenteral copper administration since 10 days of age. Although he gradually appeared to deteriorated mentally and developmentally and developed West syndrome at eight months of age, he had no convulsive seizures until four years of age. At four years of age, tonic spasms, which tended to be i.e. pseudoperiodic appeared. He had two types of tonic spasms, flexor spasms and extensor spasms. An ictal EEG also revealed different patterns, including diffuse desynchronization superimposed over the low voltage fast activities of during the flexor spasms and fast activities appeared only during extensor spasms. Both of these ictal events were dominantly in the left hemisphere on a EEG and each of the tonic spasms was easily controlled with phenytoin. The possibility must be entertained that the presented tonic spasms may have been partial seizures.

Key words : Menkes kinky hair disease — partial seizures — pseudoperiodic tonic spasms

Menkes kinky hair disease (MKHD) is an X-linked neurodegenerative disorder characterized by impaired malabsorption of copper and abnormal concentrations in multiple organs.[1-3] Since the first description by Menkes et al.,[1] there have been many reports in the literature. In 1972, Danks and his co-workers observed that there was a deficiency in intestinal copper absorption in patients with MKHD and recommended treatment with parenteral copper.[4] Since then, many attempts have been made to treat MKHD with copper administration but there has been no demonstrable beneficial effect on the progressive neurological deterioration that occurs with MKHD.[5,6] In addition, recent investigators have proposed that such neurological damage and defective copper utilization may exist from the prenatal period.[7] It is known that there are various kinds of seizures and usually the first seizure, which occurs at the age of two to five months tends to be intractable.[8,9] However, detailed chronological EEG studies have not been carried out. Here we report on a six-year-old child with MKHD who had received parenteral copper therapy since 10 days of age presenting with pseudoperiodic tonic spasms during the clinical course.

八木信一，片岡直樹，三浦　洋，水田　俊，守田哲朗

CASE REPORT

The patient was the product of a 34 weeks pregnancy. His birth weight was 1490 g and his Apgar score was 8 at 1 min. He was admitted to our hospital because he was premature and had mild respiratory distress, general hypotonia, and peculiar hair. The diagnosis was based on his serum copper and ceruloplasmin levels and also on his family history (his cousin had MKHD). Since 10 days of age, he had received parenteral copper therapy. Although he seems to be well until five months of age, at that time a generalized convulsive seizure occurred. Subsequently he developed West syndrome at eight months of age and his EEG worsened, exhibiting hypsarrhythmia. ACTH therapy was not successful, but sodium valproate and clonazepam were effective. After West syndrome occurred, he appeared to be mentally and developmentally retarded. He sometimes required hospitalization because of respiratory and/or urinary tract infections until four years of age. At that time he suffered from pneumonia, mechanical ventilation was required for one month because of respiratory and heart failure. Thereafter, pseudoperiodic tonic spasms occurred, and although the doses of clonazepam were increased, the seizures continued. The tonic spasms resembled those of West syndrome. Surprisingly, his tonic spasms disappeared when treated with phenytoin. Subsequently, no further seizures were seen. However he had respiratory failure due to pneumonia again at six years of age and died.

Chronological EEG findings during the course and clinical features of the tonic spasms

Six days after birth, an EEG including a sleep polygraph revealed abnormal sleep patterns which made it difficult to distinguish between active sleep and quiet sleep. At one month of age, his EEG revealed low voltage irregular slow waves with delta brush, and trace alternant was seen on quiet sleep EEG records at three months of age. No definite paroxysmal discharges were seen until five months of age. However, rhythmic activity appropriate to his age was scanty. At five months of age, diffuse irregular spike and waves appeared concomitant with single generalized convulsive seizure and, at eight months, his EEG exhibited hypsarrhythmia. Although no seizure discharges were seen in either his waking and sleep EEG records after the disapperance of West syndrome, his EEG showed slow and fast waves, i.e., mixed dysrhythmia, during the clinical course. No sleep spindles appeared, however, at four years of age when the pseudoperiodic tonic spasms began, he had multiple independent spike foci on his EEG (Fig. 1). These EEG abnormalities were dominantly in the left posterior head area. There were two types of tonic spasms, flexor spasms and extensor spasms, and he sometimes described laughter preceding the onset of each spasm.

The appearance of tonic spasms was confined to the waking state one flexor spasms had no clusters of attacks, but at least one extensor spasm occurred every 7 to 20 seconds and these clusters were composed of about 10 to 15 spasms. The total duration of the pseudoperiodic tonic spasms varied from 70 seconds to several minutes. Ictal EEG findings associated with these tonic spasms showed different patterns, such as left posterior sharp waves followed by desynchronyzation patterns superimposed 20-25 c/s fast activities

of flexor spasms (Fig. 2) and fast activities marked only during extensor spasms (Fig. 3). After treatment with oral phenytoin, both of these EEG abnormalities and the ictal events disappeared. Although paroxysmal EEG abnormalities were not seen, his EEG demonstrated low voltage slow waves, i.e., dysrhythmia.

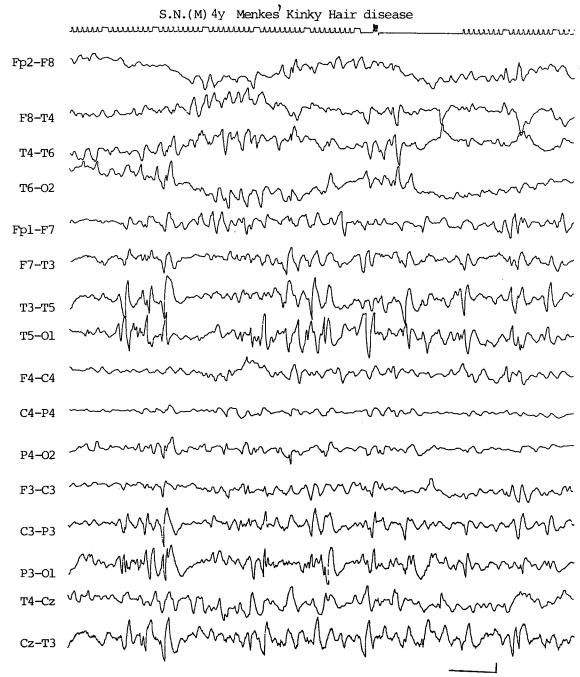

Fig. 1. At the time of tonic spasms appeared, interictal EEG shows multiple independent spikes foci dominantly in the left posterior head area.

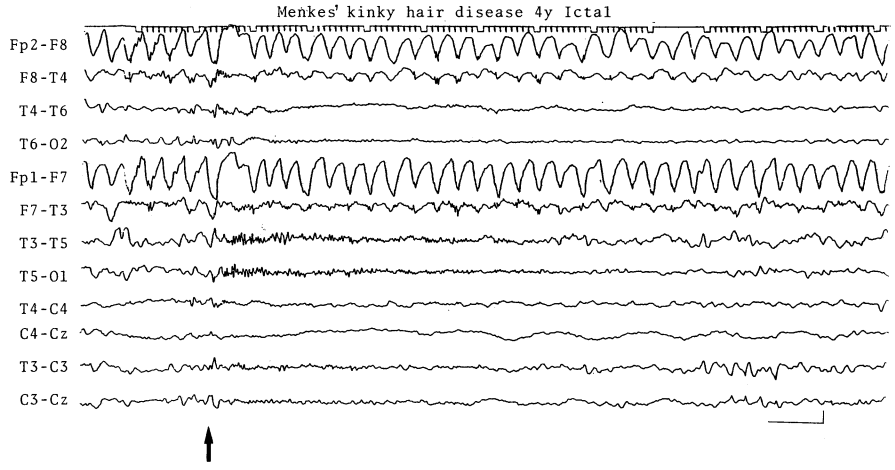

Fig. 2. Arrow indicates the onset of flexor spasms, EEG shows left posterior sharp waves followed by desynchronization patterns superimposed 20-25 c/s fast activities.

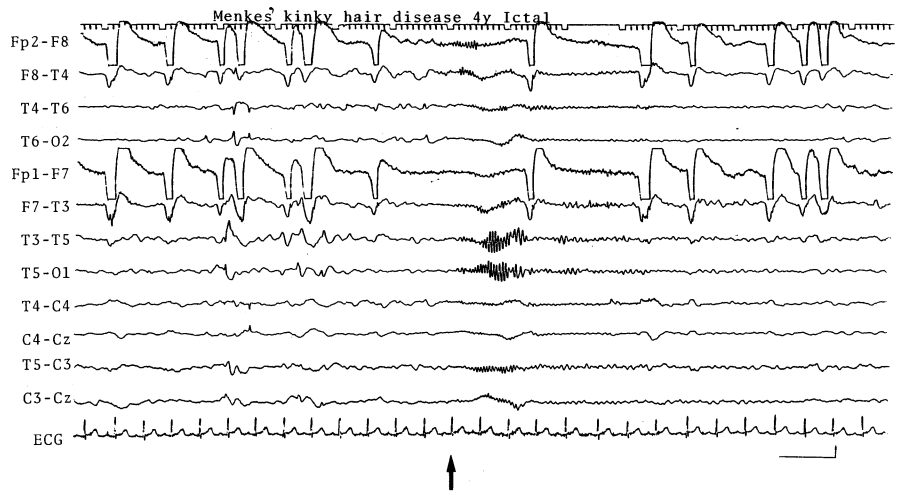

Fig. 3. Arrows indicate the onset of extensor spasms, ictal EEG shows 25 c/s low voltages fast activities.

DISCUSSION

Although many studies involving biochemical investigations of copper and catecholamine metabolism have been reported,[2-4,10] the pathogenesis of MKHD has been controversial.

Recently, several variants of MKHD have been recognized including cases presenting with ataxia, mild mental retardation and/or extrapyramidal symptoms[11] but most cases have been appeared to be mentally and developmentally retarded despite copper administration. On the other hand, it is well known that various kinds of convulsive seizures occur in MKHD.[8,9]

Long term follow-up EEG studies, however, have been scanty until now. Generally, the first seizures occur at the age of two to five months and tend to be intractable minor seizures, such as focal motor, myoclonic and/or brief tonic seizures. In detailed neurophysiological studies by Friedman and his coworkers, reported to be the first seizures were also usually focal and often prolonged.[9] However, later brief tonic spasms were the most usual type of attacks. Although there were few ictal EEG findings from these attacks, infantile spasms should be considered after the age of four to five months. If such seizures of myoclonic and/or brief tonic spasms occur in the early clinical course, detailed EEG studies should be required to make a differential diagnosis of either early myoclonic epileptic encephalopathy[12] or early infantile epileptic encephalopathy with suppression burst.[13]

During the early clinical courses in MKHD, EEG usually exhibit focal and/or multifocal paroxysmal discharges with slow background activities and there later become diffuse abnormalities.[8,9] At the time brief tonic spasms began, hypsarhythmic patterns are recognizable. Additionally, specific sleep patterns such as bicentral sharp waves and sleep spindles are scanty during the course. In the present case, sleep polygraph records at six days after birth exhibited abnormal sleep patterns which made it difficult to distinguish between active sleep and quiet sleep. These EEG findings suggest the occurrence of brain damage before birth. Therefore detailed sleep polygraph analysis should

be done if no paroxysmal EEG abnormalities are detected in the early clinical course.

To our knowledge, there have been no reports of late onset pseudoperiodic tonic spasms in MKHD. Of additional interest, is the fact that the presented tonic spasms disappeared when treated with PHT and an ictal EEG showed focal features followed with desynchronization patterns of flexor spasms and/or the fast activities of extensor spasms, especially marked the left hemisphere. The authors believe that such tonic spasms may evolve from partial seizures. Recently, Yamamoto and his co-workers described four cases of partial seizures evolving into infantile spasms,[14] two cases showing asymmetrical hypsarhythmia and one with frequent irregular polyspikes and waves on an interictal EEG. They proposed administration of carbamazepine as the most effective treatment. The pathophysiology of these spasms is unclear but brainstem abnormalities have been suspected.[14] Gobbi *et al.*,[15] however, noted new condition characterized by episodes of periodic spasms accompanied by periodic EEG complexes. In the EEG, each spasm coincides with diffuse high voltage slow waves superimposed over fast activities. Between spasms the level of vigilance is impaired or behavior changes occurs, and focal features followed by periodic events were recognized. They proposed that these findings may be considered as a particular type of partial seizure. The clinical features consist of bilateral and asymmetrical spasms occurring in periodic sequence and often involve the axial muscles with rising of the shoulders and adversion of the eyes and head with rectus type facial grimaces. Several brain disorders related to a genesis of corpus callosum, lissencephaly, tuberous sclerosis and clastic lesions have been recognized. Although our case with MKHD exhibited a different ictal EEG, the features tonic spasms experienced resembled the clinical description of Gobbi. Patients with these characteristic spasms may not have a common specific underlying brain disease, but various kinds of disturbance in the function of certain brain structures may contribute to periodic spasms. The authors believe that further study will be necessary to clarify the pathophysiology of periodic spasms and also the possibility that underlying metabolic diseases like MKHD or others may be involved should be recognized.

REFERENCES

1) Menkes, J.H., Alter, M., Steigleder, G.K., Weakley, D.R. and Sung, J.H.: A sex-linked recessive disorder with retardation of growth, peculiar hair, and focal cerebral and cerebellar degeneration. Pediatrics **29**: 764-779, 1962
2) Horn, N.: Copper incorporation studies on cultured cells for prenatal diagnosis of Menkes disease. Lancet **1**: 1156-1158, 1976
3) Williams, D.M. and Atkin, C.L.: Tissue copper concentrations of patients with Menkes kinky hair disease. Am. J. Dis. Child. **135**: 375-376, 1981
4) Danks, D.M., Cambell, P.E., Stevent, B.J., Mayne, V. and Cartwright, E.: Menkes kinky hair syndrome. An inherited defect in copper absorption with widespread effects. Pediatrics **50**: 188-201, 1972
5) Garnica, A.D., Frias, J.L. and Rennert, O.M.: Menkes kinky hair syndrome: Is it treatable disorder? Clin. Genet. **11**: 154-161, 1977
6) Garnica, A.D.: The failure of parenteral copper therapy in Menkes kinky hair syndrome. Eur. J. Pediatr. **142**: 98-102, 1984

7) Nooijen, J.L., De Groot, C.J., Von Den Harmer, C.J.A., Monnens, A.H., Willemse, J. and Niermeijer, F.: Trace elements in three patients and a fetus with Menkes disease. Effect of copper therapy. Pediatr. Res. **15**: 284-289, 1981
8) Singh, S. and Bresnan, M.J.: Menkes kinky hair syndrome (Triocho-poliodystrophy). Low copper levels in the blood, hair, and urine. Am. J. Dis. Child. **125**: 572-578, 1973
9) Friedman, E., Harden, A. and Pampiglion, K.M.G.: Menkes disease: neurophysiological aspects. J. Neurol. Neurosurg. Psychiatr. **41**: 505-510, 1978
10) Hoeldtke, R.D., Cabanaugph, S.T., Hughes, J.D., Mattis-Graves, K., Hobnell, E. and Grover, W.: Catecholamine metabolism in kinky hair disease. Pediatr. Neurol. **4**: 23-26, 1988
11) Nadal, D. and Baerlochoer, K.: Menkes disease: long-term treatment with copper and D-penicillamine. Eur. J. Pediatr. **147**: 621-625, 1988
12) Aicardi, J.: Early myoclonic encephalopathy. *In* Epileptic syndromes in infancy, childhood and adolescence, ed. by Roger, J., Dravet, M.B., Dreifuss, F.E. and Wolf, P. Jon Libbey Eurotext Ltd, London & Paris. 1985, pp. 12-21
13) Ohtahara, S.: Clinico-electrical delineation of epileptic encephalopathies in childhood. Asian Med. J. **21**: 7-17, 1978
14) Yamamoto, N., Watanabe, K., Negero, T., Furune, S., Takahashi, I., Nomura, K. and Matsumoto, A.: Partial seizures evolving to infantile spasms. Epilepsia **29**: 34-40, 1988
15) Gobbi, G., Bruno, L., Pini, A., Rossi, P.G. and Tassinari, C.A.: Periodic spasms: an unclassified type of epileptic seizure in childhood. Dev. Med. Child. Neurol. **29**: 766-775, 1987