行政院國家科學委員會專題研究計畫　成果報告

家族陣發性動作引發性舞蹈指痙症在臺灣的臨床表現與基因分析

計畫類別：個別型計畫
計畫編號：NSC94-2314-B-039-010-
執行期間：94 年 08 月 01 日至 95 年 07 月 31 日
執行單位：中國醫藥大學附設醫院小兒科

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報告類型：精簡報告

處理方式：本計畫可公開查詢

中　華　民　國 95 年 10 月 24 日

Clinical Manifestation and Carbamazepine Treatment of Patients with Paroxysmal Kinesigenic Choreoathetosis

陣發性動作引發舞蹈徐動症之臨床表現及癲通治療成效

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Running title: Paroxysmal kinesigenic choreoathetosis and carbamazepine

Abstract：Paroxysmal kinesigenic choreoathetosis (PKC) is characterized by episodes of brief dystonia or choreoathetosis which is induced by sudden movement. We report the clinical manifestations and efficacy of treatment with carbamazepine in familial PKC. Seven patients from two families were diagnosed with PKC. The most common precipitating factors in our patients were sudden movement, anxiety and stress. The mean age of the first attack was around early puberty, and the symptoms became remarkable during early adulthood. Interictal single-photon emission computed tomography of the brain revealed abnormal perfusion of regional cerebral flow in either the basal ganglia or thalami in most of the patients. Four of seven patients were prescribed low dose of carbamazepine (1.5-2.0 mg/kg/day); the follow-up period ranged from 14 to 30 months. The patients who received carbamazepine treatment became attack-free without decline in school performance. The results suggest that the prognosis of PKC is a relatively benign entity due to spontaneous resolution since adulthood, and a low dose of carbamazepine is sufficient to manage PKC. Abnormal cerebral perfusion flow over the basal ganglia or thalami in these patients leads us to believe that PKC is a form of extrapyramidal disorder.

Key words：paroxysmal kinesigenic choreoathetosis, familial, dystonia, extrapyramidal disorder, carbamazepine

Introduction： Paroxysmal kinesigenic choreoathetosis (PKC) is characterized by brief attacks of dystonia or choreoathetosis that are usually provoked by sudden movements. The age of onset is around early stage of teenagers.[1] Sudden movement after a prolonged rest period is the most common precipitating factor. The duration of the attacks is usually brief, lasting only seconds to 5 minutes.[2,3,4,5] They may occur many times each day, but the frequency and severity of the attack seem to decrease with age.

Brain imaging and electroencephalography (EEG) of these patients are usually normal.[1,6] However, some studies have suggested that PKC is a type of reflex epilepsy. [7,8,9] The pathophysiological mechanism of PKC remains not well understood. Ion channelopathy has been suggested because the disease responded to ion channel blockers well.[10] Patients with PKC have been reported to respond well to variable anticonvulsants, particularly carbamazepine (CBZ) .[1,4,6,11] We report our series of patients with clinical manifestations of familial PKC that responded well to low dose CBZ.

Material and methods：We reviewed our patients from two families with familial PKC (Figure 1) at the China Medical University Hospital between 2000 and 2003. Among these two families, a total of seven patients were diagnosed with PKC. The study was approved by the Ethics Committee of the China Medical University Hospital, Taichung, Taiwan. All patients underwent a detailed interview and neurological assessment by a pediatric neurologist. The diagnosis of the entity was based on brief, paroxysmal and kinesigenic movement in each episode.[1,2,4] Personal data, family history and characters of the attacks were obtained by means of questionnaires and personal interviews.

Six of the seven patients with PKC underwent interictal EEG recording and magnetic

resonance imagings (MRI) of the head, and all seven patients were arranged for interictal single-photon emission computed tomography (SPECT) perfusion imaging of the brain.

Three of the seven patients (A-1, A-2, B-1) spontaneously remissed at the time they visited us, and the remaining four were prescribed CBZ as monotherapy. A dosage of 100 mg per day was prescribed for the four patients. The follow-up period ranged from 14 to 30 months.

Results：The mean age at onset of these seven patients with PKC was 11.7 years (ranging from age 10 to 13 years) (Table 1). The most common precipitating factors in our patients were sudden movement or postural change, especially after a period of rest. All patients of family A had similar precipitation factors, including stress, anxiety, or laughing loudly. Aura could also occur in all the members of family A. In family B, the major precipitation factor was sudden body movement. Each attack consisted of either dystonia or choreoathetosis in the limbs, and usually occurred bilaterally or alternately. The duration of attacks was usually less than 10 seconds. All patients were alert during the attacks, and no neurological deficit between attacks in each patient was found.

The interictal EEG recordings and brain MRIs of the patients were all normal. The rhythms of the EEGs were symmetrical without partial or generalized slowing, and epileptic discharge could not be found in each of the interictal EEGs. No structural lesions of the head were found by the MRI. Investigations using interictal SPECT in all seven patients were performed before treatment. The results of interictal SPECTs revealed regional hypoperfusion over the basal ganglia or thalami.

PKC in four adolescents completely resolved after CBZ 100mg/day treatment (range 1.5 to 2.0 mg/kg/day). No adverse effect of CBZ treatment was observed during the

follow-up period (range from 14 to 30 months). During treatment period, patients attempted to withdrawal the medicine, but the symptoms relapsed.

Discussion：PKC is the most frequent form of paroxysmal dyskinesia. Demirkiran and Jankovic[2] classified the etiologies of PKC into idiopathic and secondary. They reported PKC in 13 patients with a mean age at onset of 21.4 years. Among 13 patients, 9 were idiopathic and the remaining 4 had PKC associated with trauma, stroke or encephalitis. In our study, all of our patients were idiopathic and presented as autosomal-dominant inheritance.[1,4,6] Demirkirin and Jankovic proposed the modified classification of paroxysmal dyskinesias into four main subgroups, based chiefly on precipitating events. Kailash[12] reviewed the clinical feature and mapped loci of genes of familial paroxysmal dyskinesia condition. We summarized this disorder in Table 2.

The clinical features of our patients resembled the cases reported previously, including precipitating factors**,** patterns of attack and the age of onset.[1,2,4,5,6,13] Overall, the members in the same family had clinical features similar to those of the individuals in the literature. As in our families, sudden movement provoked the attacks of all those cases. However, the symptoms may present with anxiety or laughing loudly in family A.

A controversial issue is the pathophysiology of involuntary movements in PKC. It is still uncertain whether the symptoms are related to epileptic seizure or are dysfunction of the basal ganglia.[14,15,16] It has been proposed by some that this disorder is an epileptic syndrome based on the prodromata preceding the attacks, and the way the disease responds to anticonvulsants. Abnormalities of interictal EEGs of patients with PKC that have been reported included sporadic epileptic discharges or slow rhythms.[7,8,9] In our study, six of the seven patients underwent interictal EEGs, and none of those recordings showed

abnormalities. Also, the consciousnesses during attacks were all preserved. Involuntary movements in each episode have also promoted some researchers believe that PKC is an extrapyramidal disorder. Recently, cerebral perfusion scanning has been applied to measure the perfusion of brain in patients with PKC. Perlmutter [15] reported a patient with hemidystonia, in whom an abnormality of the contralateral basal ganglia was seen in positron emission tomography. Ko [14] demonstrated increased perfusion of the basal ganglia in PKC patients by using ictal ^{99m}Tc ethyl cysteinate dimmer SPECTs. All of our patients underwent interictal SPECTs, which showed variable perfusions in basal ganglia, thalami or temporal regions. The phenomenology of PKC and the abnormality of cerebral blood flow in basal ganglia or thalami have led us to believe that PKC is an extrapyramidal disorder.

Patients who have PKC attacks seem to respond well to anticonvulsants, including phenytoin, volproate, oxacarbamazepine, lamotrigine, and especially CBZ.[5,6,11,17,18] The mechanism of anticonvulsants is blockade of ion conduction through the voltage-dependent ion channels of the neuron. Although the physiology of PKC is still uncertain, ion channelopathy is considered because previous studies reported patients with PKC were sensitive to various ion channel blockers, such as CBZ.[6,17] CBZ is widely used because it is inexpensive and broad-spectrum in seizure controls. A CBZ dosage of 100mg /day was effective in controlling PKC in our study. Four of seven patients who received CBZ as a trial experienced dramatic effect on the control of the attacks. The therapeutic dose ranged from 1.5 to 2 mg/kg/day, which was lower than that in seizure control. None of our patients treated with CBZ had intellectual impairment or decline of school performance during the follow-up. The other three untreated patients remissed

spontaneously after puberty also maintain a good quality of daily life.

We conclude that PKC is a benign, self-remissionable neurological condition. The abnormalities observed on SPECTs suggest that PKC may be an extrapyramidal disorder. Unlike other subtypes of paroxysmal dyskinesias, patients with PKC usually respond well to CBZ. Low dose of CBZ is sufficient to provide a good control of PKC; it is an inexpensive and convenient treatment for PKC.

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Members of family	A-1	A-2	A-3	A-4	B-1	B-2	B-3
Age (years)	44	36	16	13	46	19	18
Gender	Male	Female	Male	Female	Female	Male	Male
Age of onset (years)	13	13	11	13	10	11	11
Aura	+	+	+	+	-	-	+
Clinical feature							
Dystonia	+	+	+	+	+	+	+
Choreoathetosis	+	-	+	+	-	-	-
Distribution							
Bilateral or alternating sides	+	+	+	+	+	+	+
Extremities	U and L	L	U and L	U and L	U and L	U and L	U and L
Frequency	Variable,1-2 times/day	Variable,1-2 times/day	2-3 times/day	2-3 times/day	1-2 times/ day	4-5 times/day	4-5 times/day
Precipitating factor							
Sudden movement	+	+	+	+	+	+	+
Anxiety	+	+	+	+	-	-	-
Laughing loudly	-	-	-	+	-	-	-
SPECT	Hypoperfusion over left basal ganglia and temporal lobe	Hypoperfusion over left frontal and temporal lobe	Hypoperfusion over left temporal lobe	Hypoperfusion over left basal ganglia and temporal lobe	Asymmetrical thalami perfusion	Bilateral thalami hypoperfusion	Bilateral thalami hypoperfusion
EEG/MRI	normal	Not done	normal	normal	normal	normal	normal
Dose of CBZ/body weight	No prescribed	No prescribed	100mg per day/57kg	100mg per day/50kg	No prescribed	100mg per day/66kg	100mg per day/61kg
Response to CBZ			effective	effective		effective	effective
Follow- up duration (months)	Spontaneous remission at 18 Y/O	Spontaneous remission at 18 Y/O	30	30	Spontaneous remission at 20 y/o	14	14
Side effect to CBZ	-	-	none	none	-	none	none

Table-1:Clinical summary of 7 patients with paroxysmal kinesigenic choreoathetosis.

SPECT : single-photon emission computed tomography EEG: Electroencephalogram MRI: magnetic resonance imagings. CBZ: carbamazepine. U: upper limbs L: lower limbs

Classification	Clinical manifestation	Precipitating factor	Chrosome/inheritance	Response to CBZ /channelopathy
PKC	Short-lasting involuntary movement	Sudden movement	16p12-q12 1611.2-q12.1/AD	Well/ion channel
PNKD	Long duration attacks up to 6 hours	Alchol, caffeine,fatigue	2q33-5 1q/AD	No response/not known
PED	Lasting up to 1-2 hours	Period of exercise(5-15mins)	16p12-11.2/AD	No response/not known
PHD	Awaken with cry and involuntary movement	Occurs during sleep	20q13 15q24/AD	No response/not known

Table-2.The classification and clinical manifestation of paroxysmal dyskinesias.

PKC: Paroxysmal kinesigenic choreoathetosis PNKD:Paroxysmal non-kinesigenic choreoathetosis. PED: Paroxysmal exercise-induced dystonia PHD: Paroxysmal hypnogenic dyskinesia