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Original Articles

Retrospective Study of Idiopathic Paroxysmal Kinesigenic Dyskinesia in Children: A Rare and Benign Neurological Disorder Commonly Being Misdiagnosed or Overlooked

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Abstract

Objective: To investigate the clinical characteristics and treatment outcome of idiopathic paroxysmal kinesigenic dyskinesia (PKD) in Chinese paediatric patients. ***Method:*** This was a retrospective study of thirteen patients with a diagnosis of idiopathic paroxysmal kinesigenic dyskinesia that was followed up at a regional hospital between 2003 and 2008. ***Results:*** A total of thirteen patients with idiopathic PKD were reviewed, all were Chinese. Six patients (46%) had a positive family history of PKD. The male-to-female ratio was 3.3:1, and a higher male preponderance rate of 6:1 was noted among the sporadic cases. Ten patients (77%) presented with dystonic attacks. All cases were initially diagnosed as other medical conditions such as focal epilepsy, motor tics, muscle spasm or psychogenic disorder. Response to low dose carbamazepine (100-200 mg daily) was excellent among the treated patients. The exact pathophysiologic mechanism in PKD was not well documented, and it was postulated that basal ganglia dysfunction or mutation in central nervous system ion channels were the major ones causing this paroxysmal disorder. ***Conclusion:*** The clinical characteristics of childhood idiopathic paroxysmal kinesigenic dyskinesia in the Chinese population are very similar to previous published data, with the exception that in our study, a higher male to female ratio and a higher proportion of patients with initial presentation of dystonia are noted. Clinicians often encounter difficulty in recognising and diagnosing the disorder in the local setting. There is a need to enhance the medical professionals' awareness of this disorder in which treatment is highly effective and misdiagnosis will either delay treatment or put patients on unnecessary investigations. Early referral to specialist is advisable.

Key words Carbamazepine channelopathies; Epilepsy; Movement disorders; Paroxysmal dyskinesias

Introduction

Paroxysmal dyskinesia is a heterogeneous group of childhood onset movement disorders characterised by transient, episodic attacks of involuntary movements and postures without loss of consciousness.[1,2] According to the classification proposed by Demirkiran and Jankovic[3] in 1995, paroxysmal dyskinesia was further classified into four categories based on the precipitating factors: paroxysmal kinesigenic dyskinesia (PKD), paroxysmal nonkinesigenic dyskinesia (PNKD), paroxysmal exercise-induced dyskinesia (PED) and paroxysmal hypnogenic dyskinesia (PHD). Among them, PKD is the most common form of paroxysmal dyskinesia. PKD can further be classified as idiopathic, either familial or sporadic, or secondary depending on the underlying aetiology.[1-4]

PKD as a group is a rare disorder. It is very frequently misdiagnosed as epilepsy, tics or psychogenic conditions.

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The clinical symptoms are intermittent, and in between the attacks, there are no neurological signs. Therefore, the diagnosis of this condition is solely based on history. Majority of the studies are focused on adult patients and other ethnic groups. Case series among children and adolescents are very limited. Recent series on Han Chinese mainly focus on familial cases.[5] We have performed a retrospective review on our cohort of patients with idiopathic paroxysmal kinesigenic dyskinesia, including both sporadic and familial cases, over a five-year period. We aim to look into the demographic data, clinical characteristics and treatment outcomes of idiopathic PKD among Chinese paediatric patients.

Method

We retrospectively reviewed thirteen patients with idiopathic paroxysmal kinesigenic dyskinesia seen at the Department of Paediatrics and Adolescent Medicine of a regional hospital between 2003 and 2008. Cases were identified from the Clinical Management System at the regional hospital and data were retrieved from the medical records supplemented by direct patient interviews. All patients were diagnosed by paediatric neurologists and they were followed up for more than one year. The following data were obtained: baseline demographics data of patient, age of onset, trigger and precipitant of the attack, presence of aura, duration, frequency and semiology of the attacks, alteration of consciousness during the attacks, neurological examinations in between the attacks, reasons and sources of the referrals and time spent in obtaining the correct diagnosis after referral, course of illness, treatment responses, associated neurological disorders and family history of paroxysmal dyskinesia.

The abnormal movements were either directly observed or videotaped. At least one video electroencephalogram (EEG) was performed in all patients, and the attacks were recorded in nine patients. The videotapes were reviewed and the classifications of the types of movement disorders were re-confirmed. Magnetic Resonance Imaging (MRI) of brain was done in every case. Other investigations included serum copper and ceruloplasmin levels, fasting lactate and pyruvate levels and routine metabolic screening such as urine for reducing substance, amino acids, organic acids, purines and pyrimidines in order to rule out secondary causes.

Results

Baseline Demographics

There were thirteen Chinese patients, ten males and three females, with the male-to-female ratio 3.3:1. The mean age of onset was 10.4 years (range = 7-14 years, SD = 2.4). Six had a positive family history of PKD and seven were sporadic cases. In familial cases, the male: female ratio was 2:1, but in sporadic cases, the male: female ratio was 6:1. Three familial cases also had family history of epilepsy (Table 1). All patients attended age appropriate grades in normal school.

History of Infantile Convulsion

Infantile convulsions were reported in two familial and one sporadic cases. Two had onset at four months of age and one at nine months of age. They received medical treatments in China and had good responses to anticonvulsants. Medications were stopped at age of three and there were no recurrence of seizure attacks. They all had normal psychomotor developments. The age of onset of the abnormal movement was seven, eight and eleven years respectively.

Trigger / Precipitant

The kinesigenic trigger was typically a sudden volitional movement involving the whole body, or initiation of movement such as standing or walking. All patients reported attacks triggered by sudden change of body postures. Four patients (31%) experienced attacks when they tried to get off the bus from prolonged sitting. Anxiety, stress and excitement were reported as precipitants in lowering the threshold to have more frequent attacks. Two patients (15%) reported attacks when they were being called upon during class to answer questions.

Attack Characteristics

Aura in the form of frightening feeling followed by a crawling sensation over the affected limb was reported in one patient before the clinical attack. Attacks of abnormal movements lasted less than one minute, and all patients had daily attacks, ranging from several attacks up to twenty attacks per day. Ten patients described the paroxysms as dystonia (77%), one as (8%) choreoathetosis, and the remaining two (15%) as a mixture of dystonia and choreoathetosis. Attacks were unilateral in 54%, bilateral in 38%, or both in 8%. The distributions of the attacks include upper limb (100%),

Table 1 Baseline demographic data, time spent in making correct diagnosis after referral and treatment response

Patient	Sex	Age of onset (years)	Family history of paroxysmal kinesigenic dyskinesia	Family history of epilepsy	Past medical history	Time spent in making correct diagnosis after referral	Type of treatment	Treatment response
1	M	12	Yes (Father, sister)	No	No	3 months	Carbamazepine	Good
2	F	14	Yes (Father, brother)	No	No	0	Defaulted	Defaulted
3	M	13	Yes (Mother, sister)	Yes (Maternal uncle)	No	1 month	Carbamazepine	Good
4	M	9	No	No	No	1 month	Carbamazepine	Good
5	M	11	No	No	No	1 month	Carbamazepine	Good
6	M	8	Yes (Father)	No	Infantile convulsion	2.5 years	Levodopa, carbamazepine	Complete remissions after adding carbamazepine
7	M	7	Yes (Father, paternal grandfather)	Yes (Father, paternal grandfather, paternal uncle)	Infantile convulsion	6 months	Carbamazepine	Good
8	M	11	No	No	Infantile convulsion	0	Carbamazepine	Good
9	M	8	No	No	No	7 years	Sodium valproate, carbamazepine	Complete remissions after adding carbamazepine
10	M	10	No	No	No	10 months	Refused medication	Refused medication
11	F	8	Yes (Mother, sister)	Yes (Maternal uncle)	No	0	Carbamazepine	Good
12	M	10	No	No	No	0	Carbamazepine	Good
13	F	14	No	No	No	0	Carbamazepine	Good

lower limb (92%), face and oromandibular (31%), neck (8%) and trunk (8%) (Table 2).

Reasons and Sources of the Referrals and the Time Spent in Making the Correct Diagnosis

The majority of patients were referred from the emergency departments, general outpatient clinics and private general practitioners (Figure 1). Six patients (46%) were diagnosed as focal epilepsy. Other initial diagnoses included motor tics (23%), suspected movement disorder (15%), muscle spasm (8%) and psychogenic disorder (8%) (Figure 2). The time spent in making the correct diagnosis after referral was variable. Most patients (85%) were diagnosed by the neurology team within the first six months after referral (Table 1). However, there was one patient who was seen at the clinic for seven years before being diagnosed

Table 2 Comparison of clinical characteristics in childhood primary paroxysmal kinesigenic dyskinesia

	Percentage (%)		
	Current series n=13	**Zorzi et al[6] n=13**	**Bruno et al[9] n=95**
Sex			
Male	77	46	54
Female	23	54	46
Age of onset (year)			
0-5	0	38	–
6-16	100	62	88
Family history			
Paroxysmal kinesigenic dyskinesia	46	69	67
Epilepsy	23	–	–
Past history			
Benign infantile convulsion	23	–	42
Phenomenology			
Dystonia	77	38	57
Choreiform	8	15	6
Mixed	15	46	33
Laterality			
Unilateral	54	8	36
Bilateral	38	46	35
Both	8	46	30
Distribution			
Face	31	–	–
Oromandibular	31	–	–
Neck	8	–	–
Upper limbs	100	–	–
Lower limbs	92	–	–
Trunk	8	–	–

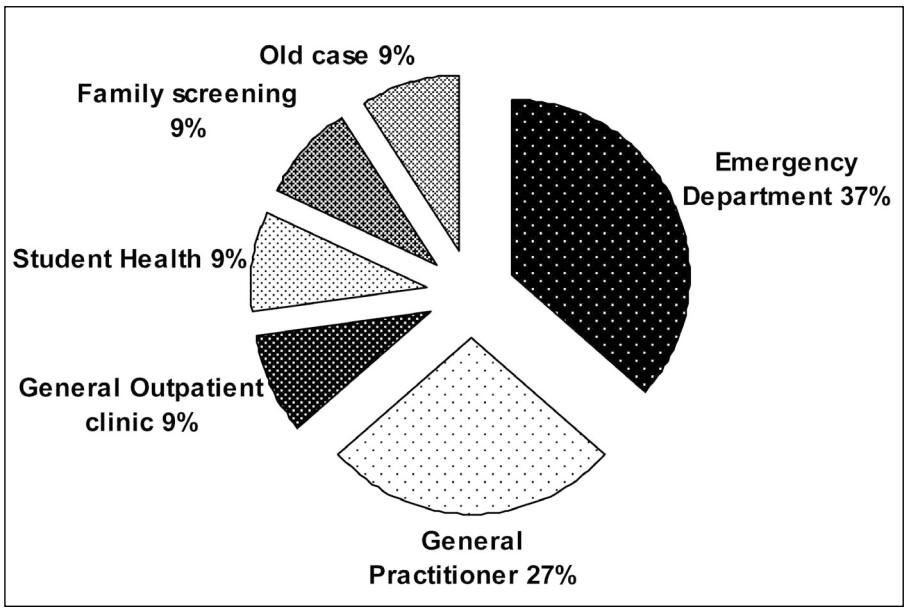

Figure 1 Referral sources.

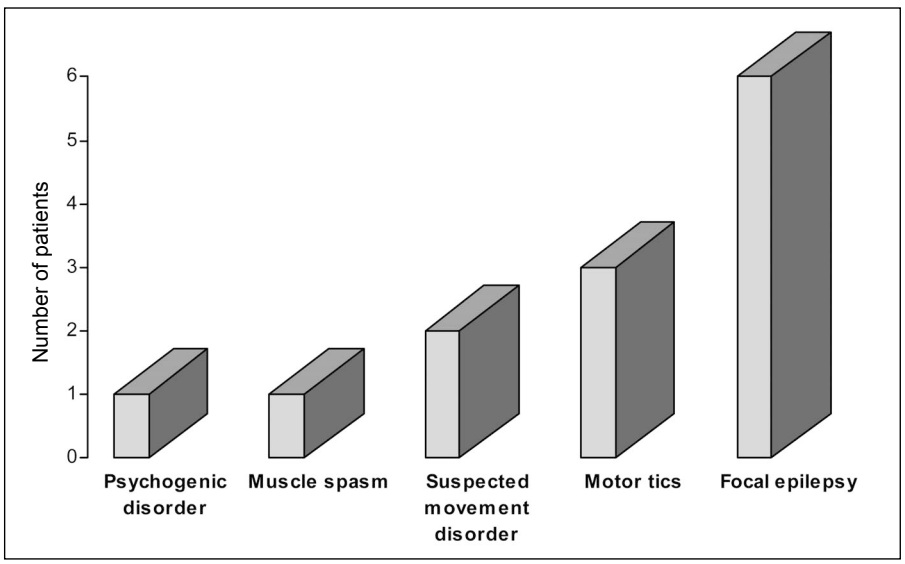

Figure 2 Referral diagnosis.

as PKD. This patient presented with episodic attacks of unilateral involuntary limb movement associated with preceding aura. He was initially treated as focal epilepsy, but repeated video electroencephalograms were normal. He was treated with sodium valproate but he only had partial response. Eventually carbamazepine was added and there was complete resolution of the attacks. This patient was later reviewed to have PKD with the identification of the kinesigenic triggers after seven years of follow up.

Investigations

All patients had at least one video electroencephalogram (EEG) performed. Abnormal movements were recorded in eight patients but no associated EEG abnormalities were noted. All had normal MRI brain. Serum copper and ceruloplasmin levels, fasting lactate and pyruvate levels, and urine for routine metabolic screening were performed in all patients and the results were normal.

Treatment Response and Outcome

Eleven (85%) patients received pharmacological treatment. One patient defaulted follow up and the other one refused medical treatment and defaulted follow up as well. Nine received carbamazepine alone (100-200 mg

daily) and all had complete resolution of the attacks. Two patients were initially given sodium valproate and levodopa respectively with partial responses. After their drug regime was replaced by carbamazepine, complete remission of attacks was noted. Of the eleven patients who received drug treatment, five relapsed when medications stopped. However, they were able to obtain complete remission after resuming the medications. Eventually all eleven patients were still on medications.

Discussion

PKD is the most frequent form of paroxysmal dyskinesia in childhood. It is characterised by recurrent episodic attacks of involuntary movements triggered by sudden voluntary movements. PKD can be further classified into idiopathic (familial or sporadic), or secondary according to the underlying aetiology.[1-4,6] Secondary PKD in children is commonly associated with basal ganglia calcifications, hypoxic-ischaemic encephalopathy, vascular lesions, postinfectious sequelae or head injury, whereas in adults, it is most commonly associated with multiple sclerosis.[1] Although the episodes are kinesigenic, they usually differ from the typical PKD in some way. Paroxysmal unilateral and axial-distribution dyskinesias, painful and hyperventilation induced attacks and presence of aura before attacks are features more commonly seen in secondary cases. In between attacks, focal deficits are frequently present.[1,7]

According to the previously reported series, idiopathic PKD usually has its onset in late childhood and early adolescence between six and sixteen years.[1] Our study similarly show that the mean age of onset is 10.4 years (range = 7-14 years, SD = 2.4). Males are more commonly affected than females, and the male-to-female ratio has been reported to be ranging from 2:1 to 4:1 according to previous epidemiological studies.[1,8] Zorzi et al[6] reported a male-to-female ratio of nearly 1:1 in their study in children. Similar findings were also reported by Bruno and his coworkers[9] (Table 2). In studies of Chinese subjects, Zhou et al[5] reported a male-to-female ratio of 2.4 to 1 in 24 childhood onset familial cases. In our cohort of patients, the male: female ratio is 2:1 in familial cases, but 6:1 in sporadic cases. A higher male preponderance rate in the sporadic cases is observed in our patients. This finding may not be significant as the sample size is small and this only represents the results of one referral centre. It is postulated that the higher expression of gene in males may account for the sex difference.[10] We also find a similar frequency of familial cases (46%) described for this condition. This is very close to the findings of other studies on the pedigree analysis.

Clinical features described in the present study are compared to other cohorts (Table 2).[6,9] Regarding the types of abnormal movements, we find a higher proportion of up to 77% of cases presenting with dystonia during the paroxysms. The natural course of PKD has not been well studied, but the attacks usually diminish with age and spontaneous remissions may be achieved.[1] However, we fail to observe this disease's course among our cohorts of patients. Majority of patients are receiving medical treatments, and five relapse when medications stop. Two patients who are not on drugs are lost to follow up. Among the pharmacological treatment, antiepileptic drugs, in particular carbamazepine, are the most effective.[6] All patients who receive pharmacological treatment in our series respond well to low dose carbamazepine (100-200 mg daily) which is consistent with other studies.[1,3,11] Other medications such as phenytoin, phenobarbitone, valproic acid, clonazepam, risperidone and levodopa are also reported to be effective.[1,7,12,13]

Diagnosis of intermittent movement disorder is difficult. Among all our referrals, most of the cases (46%) are misdiagnosed as focal epilepsy. This condition may easily be overlooked unless clinicians are well aware of the disease category of paroxysmal movement disorder. The diagnosis of PKD could be made when clinical attacks are provoked by a kinesigenic trigger. However, when focal dystonic attacks simulating tonic twitching and in particular with the presence of sensory aura complicate the clinical pictures, clinicians will tend to diagnose and treat this condition as either partial or complex partial epilepsy. Furthermore, epilepsy may be encountered in patients or family members who also have paroxysmal dyskinesias.[14] This can explain why the condition is easily overlooked by paediatricians or even neurologists who are not familiar with this condition. Video electroencephalogram telemetry is very helpful to delineate focal epilepsy and PKD, and the diagnosis of epilepsy should be reviewed in those patients with repeatedly normal EEG.

Moreover, anxiety and stress can precipitate the condition, and frequent attacks can be quite distressing and induce more stress to the patient. Sometimes patients may be mistakenly labeled as having a psychogenic disorder.[8,10] Other common alternative diagnoses in children include

motor tics, hemiplegic migraine, shuddering attacks or benign myoclonus of early infancy.[1] Other primary paroxysmal dyskinesias should also be considered. Paroxysmal nonkinesigenic dyskinesia (PNKD) is characterised by spontaneous attacks which tend to be longer and less frequent than those of PKD.[11] Attacks are not triggered by physical activities but precipitated by alcohol, caffeine, stress or fatigue. Most patients do not respond to anticonvulsants.[1,11] Paroxysmal hypnogenic dyskinesia (PHD) is characterised by the sudden awakening with a cry followed by brief involuntary dystonic or ballistic movements with no detectable EEG changes.[1,11] Some patients with PHD have also been reported to have PKD as well.[3] Paroxysmal exercise-induced dyskinesia (PED) involves attacks provoked by prolonged exercise. To distinguish between PED and PKD, the attacks of PED usually occur after 10 to 15 minutes of ongoing exertion rather than occur immediately on movement. The presentations are usually dystonic and appear in the body parts being exercised and the attacks usually disappear in 10 to 15 minutes after stopping the exercise.[14] Anticonvulsants are not useful in treating PED, but acetazolamide has shown some benefit in one reported case.[15] Association between PED and epilepsy, hemiplegic migraine and rolandic epilepsy with writer's cramp has been reported.[11,16] Therefore, it is understandable that the time spent in establishing a correct diagnosis is in the order of years and varied among clinicians. We should take a careful history and recognise the abnormal movements on physical examination or video recording in order to help in confirming the diagnosis.

The pathophysiologic mechanism of paroxysmal dyskinesia remains largely unknown. Basal ganglia dysfunction has been proposed because of the clinical features of abnormal movements, the presence of specific lesions in the basal ganglia in cases of symptomatic PKD,[17] and the abnormal findings of single photon emission computed tomography studies.[18,19] The response to levodopa may also suggest a possible alteration in the dopaminergic system.[3]

Channelopathies are also considered as the underlying pathophysiology. Channelopathies are disorders caused by inherited mutations of ion channels.[20] There is a significant overlap in clinical presentation and treatment between PKD and other paroxysmal central nervous system disorders that considered being disorders of ion channels. They all present with episodic attacks on a normal interictal background and share similar precipitating factors such as stress and fatigue in association with the attacks.[21] There is also overlap with regard to drug treatment such as the use of carbamazepine in both epilepsy and PKD.[21-24] PKD is also associated with episodic ataxia type 1 which is caused by a mutation of the potassium channel gene KCNA1 on chromosome 12.[21] As in our patients, the co-occurrence of PKD and epilepsy in some familial and sporadic cases, together with the similar phenotypes and the response to anticonvulsants support the hypothesis of channelopathy as the underlying aetiology.

Of interest are the three patients who had history of benign infantile convulsion. Benign infantile convulsion is a seizure disorder occurring in infants, usually when they are between 3 to 12 months old and is associated with normal psychomotor development and a favourable outcome.[14,25] When familial, it is an autosomal dominant disorder with incomplete penetrance, and several genes have been mapped.[14] The locus at chromosome 16 is by far the most commonly linked. The ICCA syndrome (Infantile convulsion choreoathetosis) and linkage to pericentromeric region of chromosome 16 was first suggested by Szepetowski et al[26] in 1997 which provided the first genetic evidence for shared mechanisms between benign infantile convulsion and paroxysmal dyskinesia. ICCA syndrome is a novel clinical entity derived from the association of benign infantile convulsion and the subsequent development of paroxysmal dyskinesia among the affected members in four families from northwestern France.[26] Since then, the linkage of the ICCA syndrome at chromosome 16 was confirmed in a single Chinese family by Lee et al[27] at chromosome 16p12-16q12 and six Japanese families by Tomita et al[28] at chromosome 16p11.2-q12.1. Extensive works have been undertaken in search for the genetic basis which could account for different forms of paroxysmal dyskinesia. For example, the MR1 (Myofibrillogenesis regulator 1) gene mutation has been found in paroxysmal nonkinesigenic dyskinesia.[29] Despite the existence of several PKD genetic foci, no PKD gene has been identified. The search for the PKD or ICCA gene is largely hampered by the complicated genomic architecture of the highly duplicated DNA sequences.[14] Future identification of the PKD or ICCA gene will hopefully provide important insights about the pathophysiology of paroxysmal dyskinesia and its association to benign infantile convulsions in the context of ICCA syndrome.

Major limitations of the study are its small sample size and retrospective design. However, the results from this small case series are in fact compatible with other studies which may support the validity of our results.

Conclusion

We review our children with idiopathic paroxysmal kinesigenic dyskinesia in the local setting. The clinical characteristics are very similar to previous published data, with the exception that in our study, a higher male to female ratio and a higher proportion of patients with initial presentation of dystonia are noted. Despite the complexity of the underlying aetiology, most cases are benign and responsive to the medical treatment. Clinicians often encounter difficulty in recognising and diagnosing this disorder, and a good history and high index of suspicion can minimise the misdiagnosis. The triggering factors for any "fit or faint" need careful exploration in order not to miss this diagnosis and put a stigma of epilepsy that can carry legal implications.

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