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Review

# Paroxysmal kinesigenic choreoathetosis: From first discovery in 1892 to genetic linkage with benign familial infantile convulsions

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**Abstract**

Paroxysmal kinesigenic choreoathetosis (PKC) is presently clearly designated as a familial movement disorder with autosomal dominant inheritance. We identified a family of PKC, in which 6 out of 23 members were affected, and 4 of the affected members had a history of infantile convulsions. Thus, this family was also considered as a case of infantile convulsions with paroxysmal choreoathetosis (ICCA). Video-EEG monitoring of two affected members suggested that PKC is less likely to be a form of reflex epilepsy, despite the existence of a history of infantile convulsions. Linkage analysis on eight Japanese families, including this family, defined the locus of PKC within the pericentromeric region of chromosome 16. ICCA and a form of autosomal dominant benign familial infantile convulsions (BFIC) were both mapped to the same or nearby region for PKC on chromosome 16. Additionally and quite unexpectedly, the locus of wet/dry ear wax (cerumen) was found to be located in the same region. Lastly, it was pointed out that the priority of the first discovery of PKC in the world should go to a Japanese psychiatrist, Shuzo Kure (1865–1932), who published the first detailed and almost complete description of a male patient with PKC in a Japanese medical journal in 1892.


*Keywords:* Paroxysmal kinesigenic choreoathetosis (PKC); Infantile convulsions with paroxysmal choreoathetosis (ICCA); Benign familial infantile convulsions (BFIC); Video-EEG monitoring; Locus of wet/dry ear wax; The first discovery of PKC

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## Contents



## 1. Introduction

Paroxysmal kinesigenic choreoathetosis (PKC), the most frequently described type of paroxysmal dyskinesia, is characterized by recurrent and brief attacks of involuntary movement precipitated by the sudden onset of movement. Among familial, idiopathic, and secondary cases reported thus far, familial cases in which the condition is inherited as an autosomal dominant trait are more common (Boel and Casaer, 1984). More males are known to be affected than females, and familial cases are more common in Asians than in Caucasians (Fahn, 1994; Kertesz, 1967).

Paroxysmal dyskinesias have been clinically divided into several forms. Among those, PKC and paroxysmal dystonic choreoathetosis (PDC) are the most well known and common. PKC and PDC are, though sometimes confused and misdiagnosed, clinically distinguished by certain features. PKC attacks occur more frequently, last from seconds to less than 2 min, and are induced by sudden voluntary movements, while PDC attacks last an hour or more, occur less frequently, and are precipitated by fatigue, alcohol or caffeine (Goodenough et al., 1978; Sadamatsu et al., 1999).

Although the clinical features of PKC are well described, the pathophysiology still remains a matter of controversy. Historically PKC has been ascribed to a peculiar form of reflex epilepsy. This is further substantiated by evidence that a history of afebrile infantile convulsions of benign nature is frequently noted in the same pedigree with PKC or even co-morbidly in the same individuals. Independently, a cluster of idiopathic epilepsy syndrome occurring between 3 and 12 months is now defined as benign familial infantile convulsions (BFIC), since the mode of inheritance is autosomal dominant (Vigevano et al., 1992; Caraballo et al., 2002). Consequently infantile convulsions with paroxysmal choreoathetosis (ICCA) was defined for families in which BFIC and PKC occurred within the same family (Szepetowski et al., 1997; Swoboda et al., 2000).

In this paper, we present a historical overview of the first description of PKC, and then discuss the controversial issue of the pathophysiological basis of PKC; reflex epilepsy versus dysfunction of the basal ganglia. We identified a family in which 5 of 18 members (at the time of publication in 1999) were affected with PKC, and performed video-EEG monitoring of 2 patients with PKC during attacks elicited by movements of the lower extremities (Sadamatsu et al., 1999). A further extended follow-up observation of this family revealed that 6 out of 23 members of the same family were found to be affected and 4 of the 6 affected members had a history of infantile convulsions, as reported in this paper.

Finally our results of genome-wide linkage analysis are described. Our haplotype analysis of the eight Japanese families affected by PKC defined, for the first time, the locus of PKC within the pericentromeric region of chromosome 16 (Tomita et al., 1999). Furthermore, an extraordinary story is introduced; a personal impression of the mother of a proband in our PKC family and her insistence that we follow it up led us to the mapping of the wet/dry earwax locus to the closely linked region of chromosome 16 (Tomita et al., 2000), and to the subsequent discovery of the earwax gene (Yoshiura et al., 2006).

## 2. The first case of PKC was identified in Japan

It is generally thought that the first detailed description of paroxysmal choreoathetosis was achieved by Mount and Reback (1940). In some literatures the first