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Paroxysmal Non-Kinesigenic Dyskinesia Caused by the Mutation of *MR-1* in a Large Polish Kindred

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Key Words
Paroxysmal non-kinesigenic dyskinesia · Parkinsonism · Clinical genetics

Abstract
Paroxysmal non-kinesigenic dyskinesia (PNKD) is a clinical syndrome of sudden involuntary movements, mostly of dystonic type, which may be triggered by alcohol or coffee intake, stress and fatigue. The attacks of PNKD may consist of various combinations of dystonia, chorea, athetosis and balism. They can be partial and unilateral, but mostly the hyperkinetic movements are bilateral and generalized. We present a large Polish family with 7 symptomatic members of the family in 6 generations. In all affected persons, the onset of clinical symptoms was in early childhood. All male cases showed an increase in severity and frequency of the attacks with ageing, while the only living female patient noticed an improvement of PNKD during both her pregnancies and also after menopause. In addition, at the age of 55 years, she developed symptoms of Parkinson's disease with good response to levodopa treatment.

Introduction

The first clinical description of paroxysmal non-kinesigenic dyskinesia was published in 1940 by Mount and Reback [1], who presented a case of a young man with symptoms, which they named 'paroxysmal dystonic choreoathetosis'. That patient, similarly to other 20 family members, suffered from sudden attacks of dystonic muscular spasms and choreoathetosis, which could be provoked by alcohol, coffee or tea, fatigue and smoking. The above clinical picture fits well to the classification of PNKD [2].

Recently, genetic studies allowed an identification of the gene causing this syndrome [3]. We present a large Polish family in which there were 7 known cases of PNKD in 6 generations. Our family was 1 of 8 families originally reported in which a mutation in the myofibrillogenesis regulator 1 *(MR-1)* gene caused the PNKD phenotype [3].

Case Report

The 78-year-old proband (case III:1 in the pedigree) was admitted through the Emergency Room to the Department of Neurology because of painful dystonic spasms of right extremities. No other neurological symptoms were found at admission to the hospital and interictal neurological examination was normal. The

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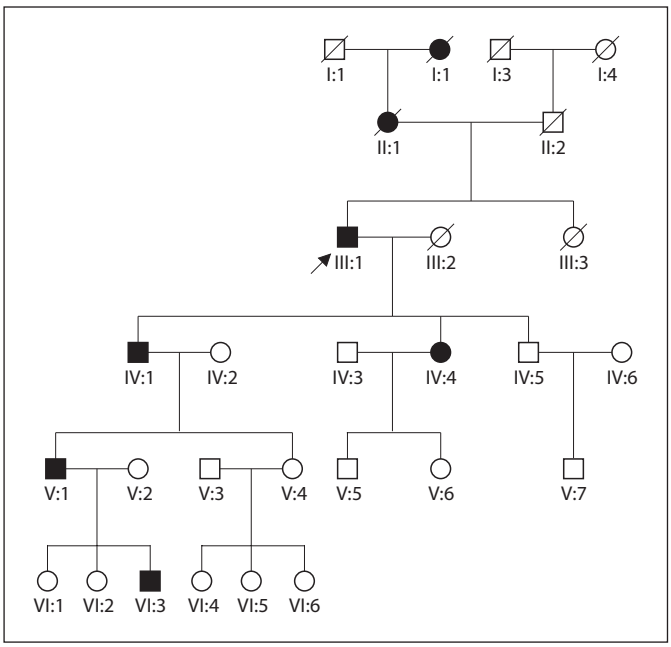

Fig. 1. The pedigree of the family. Affected members of the family are in black.

physical exam showed only moderate arterial hypertension. At admission, no information concerning the history of the disease and family was available. No significant changes, except mild cortical atrophy, were found on computed tomography of the brain. A full history, obtained from his family, suggested that he was affected with symptoms compatible with the diagnosis of PNKD since his early childhood. The pedigree of the family is shown in figure 1. All living affected members of this family were examined directly by us; the genetic study was performed on all of them, and in everyone the *MR-1* mutation was confirmed. In all affected members of the family, the symptoms appeared in childhood and they consisted of painful dystonic spasms of variable severity, localization and duration, with no other movement disorder. In cases V:1 and VI:3 the symptoms were noticed by their parents, who became aware of the problem during the first year of life. In case IV:4, the only alive female case, the attacks were usually preceded by anxiety, but this was not present in other cases. The attacks appear suddenly in most cases, without any known causative factor. However, in adult cases the attacks could be sometimes triggered by coffee and alcohol consumption. EEG performed in cases III:1 and IV:4 were normal. The attacks could last from few minutes up to several hours and their frequency increased with age. No successful preventive treatment was ever found for the affected members of the family, although several medications were tried. These included carbamazepine, valproic acid, oxazepam. Only diazepam and clonazepam were effective in interrupting the attacks, but not in their prevention. The only alive female case also demonstrated an increase in the frequency of attacks with ageing, but only until menopause when the attacks became significantly less frequent. The peculiarities of her case also include a complete disappearance of the attacks during 2 pregnancies. The attacks resumed shortly after deliveries. At the age of 55, she noticed rest tremor of her right hand. The neurological examination revealed: bradykinesia (rated as 2 points according to Unified Parkinson Disease Rating Scale; UPDRS), rigidity (1 point UPDRS) and rest tremor (2 points UPDRS) of the right upper extremity. After discussion with the patient, a decision to introduce levodopa treatment was made. After titration of the dose, she was receiving 100 mg of levodopa/benserazide slow-release preparation 4 times a day. The clinical symptoms improved to 1 UPDRS point for bradykinesia and rest tremor and 0 points for rigidity. Taking into account the clinical symptoms, together with the improvement after levodopa, the clinical diagnosis of Parkinson's disease was made. She has now been taking this dose of levodopa for more than 3 years with a good response, and no need for an increase in the dose and no motor complications. She never received postmenopausal hormone replacement therapy.

Discussion

The neurogenetic syndrome which is called paroxysmal non-kinesigenic dyskinesia (PNKD) was originally described by Mount and Reback [1]. PNKD has been recently shown to be caused by mutations in the *MR-1* gene [3, 4].

This large Polish family with a confirmed mutation in the *MR-1* gene can be regarded as a rather typical phenotype of PNKD. All of them developed their symptoms in early childhood, they all showed good symptomatic responses to diazepam, when given during the attack, and all were unresponsive to preventive antiepileptic treatment. However, unlike the majority of other reported families with *MR-1* mutations, the frequency and severity of the attacks increased with age in all male subjects [4, 5]. Our case of the female patient deserves additional comments, although the complete disappearance of the attacks during pregnancy in women with PNKD has already been reported [6]. It is also interesting that this patient noticed a decrease in severity and frequency of the attacks after menopause. Together with the onset of parkinsonian syndrome after menopause, this observation once again points to the possible role of estrogens in the pathogenesis of movement disorders. The protective role of estrogens in Parkinson's disease has been widely discussed in the literature, based on experimental [7] and clinical data [8]. The role of estrogens in Parkinson's disease is far from being clear, as stated in the recent review by Shulman [9]. The role of estrogens in induction of involuntary movements has been known for long time. More than 30 years ago, it was shown that contraceptives may cause chorea [10]. More recently, it was also suggest-

ed that estrogens may affect the clinical course of spasmodic torticollis [11]. In our patient, both pregnancy and menopause diminished the attacks of PNKD. On the other hand, after menopause she began to have parkinsonian syndrome. It is difficult to determine, based only on clinical grounds, if this was just a simple coincidence of idiopathic Parkinson's disease in a patient with PNKD. It is interesting, though, that the changes in her estrogens status were able to influence her involuntary movements. We believe that this clinical observation adds to the discussion of the possible role of estrogens in motor control.

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