CASE REPORT

Paroxysmal exercise-induced dyskinesia diagnosed using exercise test

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ABSTRACT

Background Paroxysmal movement disorders are interesting forms of hyperkinetic movement disorders that are perplexing to the neurologist and patients. The main features are transient dystonia or chorea involving various body parts and lasting few seconds, minutes or hours depending on the subtype. The paroxysmal exercise-induced dyskinesia is associated with a gene mutation of (NM_145239.2:c.649dupC) in proline-rich trans-membrane protein 2 (PRRT2). This is found in an average of 45% of cases. Familial cases have 85% penetrance.

Case report We report a case of a 12-year old boy with intermittent episodes of abnormal movements which involved his face and / or limbs. These dyskinesias occur every few days without warning. Complete neurological examination was normal. Importantly, Magnetic Resonance Imaging head and Electroencephalography were normal in association with normal haemto-biochemistry profile. The family recorded a video for one episode of his abnormal movement. The doctor set a challenge of 20 meters racing. He excited the patient then started the race with the attendance of the parents and the nurse. Few seconds after the end of the race the development of the abnormal movement was judged by the parents and nurse who all agreed on the provocation test.

Conclusion Paroxysmal exercise-induced dyskinesia is the commonest primary episodic movement disorder which has its negative effect on the quality of life. The diagnosis and management are mainly clinical. It is of paramount importance to use simple tests (exercise test) and save the patient unnecessary worries and side effects of medications.

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INTRODUCTION

Paroxysmal movement disorders are a group of rare diseases which are mostly self-limiting and patients are essentially normal between the attacks. In a minority they are a component of the neurodegenerative illnesses but mostly they are primary in nature. Paroxysmal movement disorders can present with challenging clinical features that may be linked to a wrong diagnosis like epilepsy or functional disorders. They can be precipitated by stress, emotion, coffee or alcohol and clinical presentations can be combinations of dystonia, chorea and athetosis[1]. This represents the first category of paroxysmal movement disorders while the second is paroxysmal ataxia. The baseline theory for both is the transient channelopathy affecting the influx of electrolytes through the cell membrane of the basal ganglia neurons. This event will affect the motor control of muscle transiently leading to the distinct clinical syndromes. The subtypes include, paroxysmal kinesogenic dyskinesia (PKD), Paroxysmal non kinesogenic dyskinesia (PNKD), Paroxysmal exercise induced dyskinesia (PED) and Paroxysmal nocturnal dyskinesia (PND). When transient dystonia/athetosis occurs for few seconds

or minutes, paroxysmal kinesogenic dyskinesia (PKD) is diagnosed[2,3]. If it lasts for minutes to hours it is named PNKD. Others include PED and PND. One interesting condition here is paroxysmal kinesogenic Chorea/dyskinesia PKC/PKD. It represents brief attacks of focal, hemi or multifocal chorea/dystonia that lasts for few seconds or minutes and precipitated by sudden movement. The condition is not associated with clouding or loss of consciousness which may help differentiation from epilepsy. The frequency may be high per day. The age of onset is usually childhood and adult onset is less common. Severity and frequency of attacks tend to reduce by age. In contrast, PNKD occurs few times per year. PKD was discovered to be associated with the gene mutation[4] (***NM_145239.2:c.649dupC***) in proline-rich trans-membrane protein 2 (PRRT2)[5]. Importantly, this gene can be found in 27-65% of cases. Familial cases are linked to chromosome 16[6-9]. The disorder is either present in isolation or in combination with others like benign familial infantile epilepsy (BFIE), Infantile convulsions and choreoathetosis (ICCA), PNKD, PKND like, PED, Dravet Syndrome, West Syndrome and other headache disorders which clearly challenges the diagnostic approach[4,10]. Therefore, this was attributed to the diffuse variability and complexity in the genetic findings of these disorders[2]. There is a need to establish classification for PKC may be based on phenotype and genotype structure with utilization of genetic sequencing as some patients may present with negative PRRT2 or due to deletion of other variants[3,11].

Interestingly, exercise testing can have high clinical yield in establishing the diagnosis of PKC. It was found that exercise testing lead to increase action potentials of the muscle and increment in muscle size in these patients[12]. Therefore, some centers adopted the exercise testing with or without the genetic testing[12,13]. They recommended genetic testing only in complicated cases or when prognosis for serious conditions or genetic counseling are needed[2].

Considering the need for treatment, it exceeds the episodic motor disability in these patients. A large cross sectional survey that involved 165 PKC patients over few years used a standardized questionnaire. It concluded that these patients significantly have worse scores of anxiety, depression, phobia, and lower levels of quality of life[14]. It is quite serious to have such domains occurring in a young age and by time being untreated; this may lead to future psychiatric disturbances.

The treatment options include medications that affect the ion channels like acetazolamide, antiepileptic drugs, benzodiazepines and possibly triheptanoin. Low dose carbamazepine or phenytoin is preferred[15]. Moreover, this would reduce the risk of depression and anxiety which are prevalent in these patients[14]. The diversity in the pharmacological agents is matching the complexity of molecular bases in the basal ganglia and the genetic heterogeneity of these conditions.

This case is reported because it is one of the uncommon movement disorders and its episodic occurrence makes it so challenging and puzzling to the treating physician and families. Moreover, it is of paramount importance to make the diagnosis and exclude other mimickers. By doing this, we will save the patient a diagnostic burden and long term side effects of unnecessary medications. Such cases are important to highlight to widen the diagnostic scope for neurology trainee.

THE CASE REPORT

We report a case of a 12-year old male who was reviewed in the neurology outpatient. His parents are second degree relatives. The patient was an outcome of normal delivery at term and had uneventful neonatal period as well as developmental milestones and vaccination history. He had experienced one episode of febrile seizure at the age of 5 months. There was a family history of febrile seizures. Apart from sinusitis, he did not have chronic diseases or allergies. The patient was the youngest in the family but was not described as a demanding child or an anxious personality. At the age of 8 years, he started to have intermittent

episodes of abnormal movements which may involve variable parts of his body and or limbs. His speech was not usually affected, but his neck may develop abnormal side twisting. He clearly reported no loss of consciousness or clouding of awareness during the episodes. Moreover, there were no post episode symptoms and the parents did not observe chewing movements, starring or automatic behavior during any episode. These episodes were of variable frequency and seems unrelated to certain precipitating factors but they tended to occur more during school hours. However, they can occur also at home. The abnormal movements were not much linked to stress or exams time. The patient had good school performance and good relations to school mates and teachers. He liked to play football and share activities. Both parents had normal neurological assessment. His father related the development of episodes to the sight of the playground at school. The patient was uncomfortable with the episodes as they were causing him social embracement in the school and he could not control their emergence or modify the course. In the previous six months before his current neurological appointment he was started on Aripiprazole therapy with transient reduction of frequency for three weeks and relapse of episodes shortly after that. The parents then stopped the drug because of lack of response. The patient underwent routine blood tests including the CBC, TFT, LFT, RFT, electrolytes, Calcium, Phosphorus, Parathyroid hormone, calcitonin, and previously had a normal brain CT. Moreover, had negative K F Rings, copper and ceruloplasmin levels. On the workup for epilepsy, the patient had a brain MRI which showed normal cerebral and infra-tentorial structures. There were no frontal or temporal changes and no congenital anomalies of the brain. A standard EEG showed normal background activity and no evidence of epileptiform discharges even with hyperventilation and photic stimulation. The patient was reviewed by the psychiatrist at least once and no specific diagnosis was made.

The clinical examination was normal in regard to the general, systemic and detailed neurological examination. The video showed the patient standing and displaying abnormal limb movements involving the left side and neck. They took around one minute and disappeared. During the recording, he was able to communicate and looked cognitively intact. Hence, the diagnosis was revealed in the neurology outpatient clinic by competition racing between the neurologist and the patient in the outpatient corridor for 15 meters. The exercise test was explained to the parents and made as a challenge to the patient. A verbal consent was taken from them all as emergence of abnormal movement may occur. There was no consent for the video. Then parents were asked to standby at the start point and assess the response in regard to the previous attacks. The attending certified nurse was assigned as a second judge at mid-point. At the count of 3 the race started and the patient raced the doctor out but after less than 20 second of the end and while going back to mid-point, the patient developed sudden diffuse chorea/dystonia involving the left side of his body mainly, neck and trunk. His speech became dysarthric and he remained fully conscious, oriented and balanced. There was an associated neck twisting. By the start of the movements parents were less than one meter away from him. The abnormal movement disorder recovered fully over one minute. During this hand on observation the consciousness and orientation were never affected. Therefore, this was a clinical diagnosis of PKC as PED subtype. The choice of racing came from the father's remark about provocation by the scene of the playground at school. This may indicate the buildup of stress associated with sudden movements during football play which includes a racing challenge. Following the settlement of the PED, explanation and reassurance were sufficient for the parents and patient as serious disorders were excluded. Moreover, he was advised to use low dose carbamazepine to control the attacks especially during school time. A medical report was issued to the school to explain the benign nature of the problem and to exclude the non-epileptic attack disorder. Follow up showed a satisfactory response to the clinical management.

DISCUSSION

This protein coded by PRRT2 is involved in the synaptic neurotransmitter function in the central nervous system. The defective protein produced by the mutation seems to result in a variety of genetic disorders and not only specific for PKC as mentioned earlier[4].

This case report highlights an important diagnosis which was simply pointed out using a physical test. It is similar to the work done by Chen et al who relied on the clinical diagnosis to investigate nine cases for the genetic diagnosis. The PRRT2 gene was found in only 5 cases out of nine. This potentiates the role of the clinical diagnosis of PKC and concluded that the genetic mutation of PRRT2 is having an incomplete penetrance and may not be demonstrated in all patients (only 45%). This will reflect on the lower chance of having a genetic confirmatory testing considering the individual cost for patients. On the other hand Chen et al work confirmed the mutation in comparison to our case report[16]. The same concept was addressed in a study of Japanese patients with PKC with or without benign infantile epilepsy where not all patients had the PRRT2 mutation[10]. Hence, the clinical diagnosis has an important role in these cases which are mostly diagnosed before the request of the genetic testing[17].

This case report is similar to another case report about a young adolescent female which was thought to have a generalized tonic clonic seizure disorder and started on clonazepam and levetiracetam. Worsening of nocturnal abnormal movements brought her to re-assessment. However, the detailed clinical review diagnosed her as complex PKC and related disorders. This denotes the clinical diagnosis as a major step in the diagnostic accuracy. The difference between it and the case we report here is that the genetic analysis showed the commonest mutation. The patient was well controlled on low dose carbamazepine[7]. Other case reports depend only on the clinical diagnosis as in our case report[13], while others had negative genetic testing and typical clinical diagnosis with effective response to treatment[18]. This latter case report listed a 23-year-old female who had been misdiagnosed as epilepsy and depression. On the clinical assessment of the semiology, she was diagnosed and managed as PKC with proven outcome.

Our particular patient did not have a genetic test but the precipitation of the disorder by sudden movement, exercise and the observed semiology during the attack pillared the clinical diagnosis. A case control study of sixty patients with PKC revealed a significant difference between them and normal controls in the neurophysiological terms after exercise[12]**.** This finding potentiates the exercise test as an objective, simple and good diagnostic tool beside the subjective clinical outcome after exercise. Although exercise induced dyskinesia may be thought here but the age, history of previous multiple episodes and the sudden movement at the start of the race plus the duration suggests PKC.

CONCLUSION

The case report highlights the importance of using simple test to diagnose PKC, which may have a variable, complex and episodic symptomatology. The PKC has its negative effects on the quality of life and psychological wellbeing. A misdiagnosis or mismanagement will carry a poor response or side effects of unnecessary medications. Since 1976 till a decade ago when the gene was described, clinicians relied on their clinical assessment for the diagnosis[19]. Considering the financial resources in most of the under developed world or insurance standards, the clinical diagnosis and management will be the only solution for a majority of patients across the world. A recent updated review article concluded that despite the increase in confirmed cases genetically but the management remains largely clinical. The expert opinion in that review supported PKC to be the commonest primary episodic movement disorder[20].

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