JUVENILE PARKINSON'S DISEASE WITH A VARIANT OF PRKN GENE MUTATION IN A 47-YEAR-OLD FILIPINO MALE

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ABSTRACT

A mutation in the PRKN gene has been recognized as the primary genetic cause of Early-onset Parkinson's Disease. The autosomal recessive Juvenile Parkinson's Disease, is a rare subtype of this neurodegenerative disorder that manifests before the age of 21 years old. Studies over the years have found that there is a predominance of this condition in the Western lineage. However, in the Asian population, there is little available information because there has been few genetic testing confirmed cases to this day. This is a case of a 47-year-old Filipino male having Juvenile Onset Parkinson's Disease confirmed with PARKIN (PRKN) mutation. He presents with Levodopa-responsive slowly progressive Parkinsonian symptoms, with lower-limb dystonia as initial manifestation. This case report widens the genetic mutation loci of PARKIN in the Filipino population.

KEYWORDS

Early onset parkinson's disease, juvenile parkinson's disease, PARKIN, PRKN, levodopa responsive, autosomal recessive

1. INTRODUCTION

Parkinson's Disease (PD) is a neurodegenerative disorder that ordinarily manifests at a later time in life, with a mean age of onset at 60 years. However, a small population of younger individuals has been found to develop the cardinal symptoms of tremors, rigidity, bradykinesia. Early onset Parkinson's disease (EOPD) is a rare condition characterized as PD before the age of 60 years [1]. It is classified into two types: Juvenile and Young Onset PD. Juvenile Parkinson's disease (JPD) has manifestations before the age of 20 years old. On the other hand, Young-onset Parkinson's disease (YOPD) is considered if it presents between the age of 21 and 40 years old. Generally, EOPD patients are characterized with a slower evolution of their symptoms, with less cognitive dysfunction, and with a good response to low dosage Levodopa therapy. Some may exhibit focal dystonia during their off-states [2]. Proving its rarity, the incidence of reported cases of classical EOPDs is only around 3-7% of all cases of PD in the Western hemisphere in current literature, and only data for Central Asia has been accessible, with recent studies showing that Japan having an incidence between 0.29 and 3.3 per 100,000 persons [2]. Because it begins at an earlier age, the individual with JPD is confronted with a multitude of challenges. This can afflict them with greater psychological and financial burden since they will have to rely on pharmacologic interventions and physical therapy for a much longer time in their lives, compared to those presenting with the typical later-onset Parkinson's disease.

The purpose of this case report is to present a case of a 47-year old male, coming from the island of the Philippines, a country located in Southeast Asian the eastern rim of the Asiatic Mediterranean, with a confirmed rare case of Juvenile Parkinson's disease. He manifested with

symptoms of PD during the prime of his life, beginning at the age of 17 years. This has been confirmed with genetic testing, with a PRKN gene mutation. In this regard, we give light to the existence of this condition in the Filipino population by discussing the pathophysiology and the corresponding diagnostics and interventions for such illness.

2. CASE PRESENTATION

A 47-year-old Filipino male initially presented with lower-limb dystonia at the age of 17. Lower-limb dystonia was characterized by occasional episodes of twisting of his either foot that caused him to have multiple episodes of fall when walking and running on both even and uneven surfaces. By the age of 30, the patient was noted to have shuffling gait accompanied by slowness of movement described as having difficulty in standing up from a sitting position and picking objects from the floor with an increased tendency to fall over. Furthermore, resting tremor and task-specific tremors (e.g. holding a cup or while approximating utensils to his mouth) initially at the right hand progressing to bilateral hands. Over the years, cervical dystonia was also noted with difficulty looking sideways progressing to inability to touch his chin to his shoulders.

On neurologic examination, the patient was awake with intact cognitive functions. His mini mental status examination had a perfect score of 30 out of 30. There were no cranial nerve deficits noted. The motor examination revealed no spasticity, rigidity, atrophy, myotonia and fasciculations. The patient had full strength on all major muscle groups. There was noted bradykinesia of all limbs during finger tapping, pronation and supination of the hands and heel-tapping. He had resting tremors and task-specific tremors when placing a coin inside the cup and performing the Archimedes circle test. There was noted micrographia. He was able to stand upright, with normal cadence but with decreased heel strike. He was also noted to have decreased arm swing bilaterally. There was dystonia of the right hand characterized as extension of metacarpophalangeal (MCP) and distal interphalangeal (DIP) joint of the right thumb and index finger with flexion of the 3rd to 5th MCP (Figure 1). Patient had difficulty on heel-walking but able to do toe-walking and tandem gait without difficulty. On retropulsion test, the patient was able to attain upright posture with 2-3 backward steps, unaided upon pulling his shoulders backward. There were no pathologic reflexes elicited.

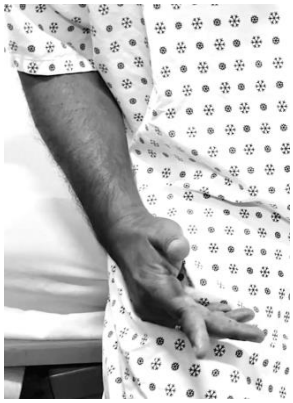

Figure 1. Dystonia of the right hand.

An Archimedes Spiral test (Figure 2) was done. For the non-dominant hand (left), the spiral was small with minimal oscillations noted at the beginning and a portion of the spiral turns became narrowly spaced at the end. Meanwhile for the dominant hand (right), the spiral was small and narrowly spaced at the beginning, with fine amplitude, multidirectional oscillations noted

approaching the end of the spiral, with widely spaced spiral turns noted as the patient tried to speed-up towards the outer section of the spiral.

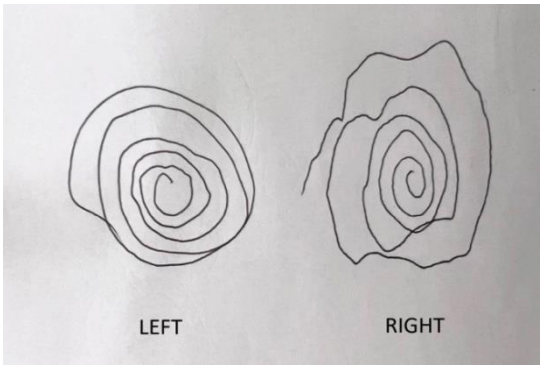

Figure 2. Archimedes spiral.

Laboratory work-up which includes level of mercury, manganese, lead, copper, ceruloplasmin and cranial MRI, were requested which revealed unremarkable findings.

Whole Exome Sequencing genetic testing was done and processed by CentoGene at Rostock, Germany, which confirmed Juvenile Parkinson Disease-2 with a missense heterozygnous PRKN mutation on p.(Cys441Arg). Two heterozygous pathogenic variants, a single nucleotide variant (SNV) and a copy number variant (CNV), were identified in the PRKN gene. The patient is currently on Levodopa/Carbidopa 100mg/25mg 1 tablet thrice a day and on physical therapy sessions twice weekly.

3. OUTCOMES AND FOLLOW-UP

Significant clinical improvement has been observed within weeks of taking his of Levodopa/Carbidopa treatment in combination with regular sessions of physical therapy which consists of a series of exercises that focused on balancing and strengthening. There was less intensity of his tremors. The patient is able to ambulate and stand up from seated position at a quicker pace with less incidences of falling out of balance. He is reported be independent on all activities of daily and instrumental living

4. DISCUSSION

Parkinson's Disease (PD), or *Paralysis agitans*, is a chronic progressive neurodegenerative disorder that increases with age, affecting about 1-2% of people over the age of 60 years, globally [3]. The clinical diagnosis, according to the Movement Disorder Society, is centered on a syndrome of motor symptoms. Rigidity, resting tremors and bradykinesia are the three fundamental motors symptoms. This may also be accompanied by instability, postural deformities, gait problems and speech disturbances, with deterioration in facial expression and dyskinesias later on as the disease advances. There are non-motor symptoms that have also been included in the criteria, which are sleep disturbances, constipation, olfactory dysfunction, cognitive decline and psychological states such as depression and apathy.

However, there has been a group of individuals that have this neurodegenerative illness at a much earlier age. The first report was done in 1981 that proved the existence of Parkin gene mutations in a case series of individuals from a consanguineous Japanese family that exhibited PD symptoms in

those younger the age of 40 [4]. In 1987, this was further supported by a cases series conducted in the United Kingdom of 60 individuals, which ultimately coined the term "Early-onset Parkinson's disease". They further subdivided this disease into two: (A) Juvenile PD begins before the age of 20 years, and (B) Young-onset PD occurs between 21-40 years old [5]. There are distinct phenotypical differences between EOPD and the typical PD. At the early disease stage, focal dystonia is more common for both JPD and YPD compared to the typically PD that usually presents with focal dystonia at the later stage of the illness. Dystonia more commonly involves the lower limb at onset for those with EOPD, especially those with the PRKN, PINK-1, DJ1 mutations. Some may also present with a hand dystonia, also known as a "writer's cramp", described as task-specific movement disturbance with abnormal hand posturing and muscle cramps that occurs while writing. Others may present with retrocollis that has been found to be receptive to sensory tricks [6].

Although rare, prompt diagnosis of EOPD has been deemed necessary. There are some genetic variants which are more responsive to pharmacologic treatments. Hence, the early detection following with an appropriate intervention is valuable because it can deter development of more severe complications. The assessment should involve work-up of other possible secondary causes of acquired EOPD such as drug-induced parkinsonism or ongoing infection. However, if there is a high suspicion of hereditary preponderance, genetic testing may be conducted right away.

There are three genes that have been documented to be involved to produce JPD namely, the PRKN (PARK2), PTEN-induced putative kinase 1 (PINK1 or PARK 6) and DJ1 (PARK7). The PINK1 and PARK2 genes, the recessively inherited mutations, have been have been shown to cause a milder, more slowly progressive type of PD, with less cognitive dysfunction and a good responsiveness to Levodopa therapy. PARK2 covers at least 500 kilobases and encodes an important ubiquitin ligase, Parkin, which is vital for the protection of the mitochondria. Parkin preserves the integrity of mitochondria from possible stressors by induction of mitophagy after oxidative stress. Along with PINK1, they work together to signal a cascade of processes that leads to mitochondrial-induced inflammation that is responsible of eliminating damaged mitochondria through the STING pathway [7]. In Parkin gene mutations, there is a loss of the normal mitophagy effect which leads to accumulation of oxidative damage, chiefly involving cells high in mitochondrial activity such as the neurons. On the other hand, PARK7, is an oncogene that works in a path parallel to the Parkin-PINK 1 to protect from mitochondrial oxidative stress, and mutation involving these gene follows a more atypical clinical course, including spasticity, behavioral disturbances, seizures, and has been shown to be less responsive to Levodopa therapy.

In this particular case, the PRKN variant c.1321T>C p.(Cys441Arg) causes an amino acid change from Cys to Arg at position 441. A heterozygous out-of-frame deletion of the exon 2 was also identified in the PRKN gene by NGS based CNV analysis and it was confirmed by MLPA performed as internal control. Combining these two heterozygous pathogenic variants produces a genetic diagnosis consistent of the autosomal recessive Juvenile Parkinson disease-2 (PARK2). This disease is slowly progressive, with a disease duration of more than 50 years reported. Clinical findings may vary: prominent involvement of the lower extremities, with atypical features of freezing gait, dyskinesias and even pyramidal signs can be appreciated. At onset, more than 75% of those with the PRKN-variant present with parkinsonian symptoms, such as bradykinesia and rigidity being the most frequent manifestations [2]. Although less common, some may have dystonia of the lower limbs at onset, as seen in this case. They may go on several years without showing any other symptoms. In several studies, it has been found that on average, it may take up to 10 years for parkinsonian symptoms to occur following an initial presentation of lower-limb dystonia [10]. Accounting to its subtlety, diagnosis is often delayed.

In a local study done in 2023, a comparison was made of six Filipino individuals with familial Parkinson's Disease [9]. Five of them were positive for PINK1 c.10140T >C(p.L347P) mutation

while only one had a heterozygous variant PRKN c.136G>T (p.A465) gene mutation, which is a different gene loci found in the present case that affected the c.1321T>C p.(Cys441Arg) loci. All of whom in the prior study presented with bradykinesia and tremors as their predominant symptoms, with a mean age of onset at 30 to 50 years old. In contrast to this present patient, that initially presented with lower-limb dystonia at the age of 17 (Table 1).

Table 1. Comparison of genetically confirmed early onset parkinsonism among Filipinos

	Index Patient	A	B	C	D	E	F
Gene Mutation	**PRKN**	PRKN	PINK1	PINK1	PINK1	PINK1	PINK1
Mutation Status	**c.1321T>C p.(Cys441Arg)**	c.136G>T (p. A465)	c.10140 T >C(p. L347P)	c.10140 T >C(p. L347P)	c.10140T >C(p. L347P)	c.10140T >C(p. L347P)	c.10140T >C(p. L347P)
Pattern of Inheritance	**Heterozygous**	Heterozygous	Homozygous	Homozygous	Homozygous	Homozygous	Homozygous
Presenting Symptom	**Dystonia**	Tremors	Bradykinesia	Bradykinesia	Bradykinesia	Tremors	Rigidity
Age at Onset	**17**	42	50	32	32	30	48

Individuals with JPD should undergo a challenge of Levodopa therapy, although it should be noted that Levodopa-induced dyskinesias (LID) are common in EOPD. Amantadine may be used as a symptomatic treatment to LID with its mechanism of action attributed to N-methyl-d-aspartate antagonism, increasing Dopamine release [8]. The use of Botulinum toxin injections has been found to be effective in addressing focal dystonia or refractory hand tremors.

5. CONCLUSION

We have presented a case of a Filipino male with a confirmed case of Juvenile Parkinson's Disease with slowly progressive course and initial symptom of lower-limb dystonia. The combination of Levodopa/Carbidopa 100mg/25mg 1 tablet thrice a day was with weekly physical therapy sessions are proven to be effective and well-tolerated in improving the manifestations. Genetic counselling for the rest of the family is recommended to be able to approach the disease with appropriate multidisciplinary interventions.

This present case report expands the genetic mutation loci of PARKIN in Filipinos. Understanding the genetic basis of Parkinson's disease in different populations can help in developing more effective treatment strategies and personalized management.

6. ETHICAL CONSIDERATIONS

The study is conducted in accordance to the accepted ethical research practice of the CARE Guidelines. An informed consent was directly obtained by the Principal Investigator using the Informed Consent for Case Reports and Certificate of Consent to Participate in English form. The study is not company sponsored or industry funded. It is investigator- initiated and the subject is a patient of the co-author of this case report. The patient's identity and personal data was not included in the study, and identifiers are removed from the manuscript. The data will be accessed securely by the Principal Investigator and will be protected from illegal or inadvertent access by other people. It will also be stored for 4 years and it will be completely deleted thereafter. There were no experimental interventions done to the subject of this study. Hence, there are only minimal risks for physical, psychological, social or economic harm since it only involves description of the case, subject's symptoms, course of illness and treatment regimens that is known worldwide. All data conveyed from this case will be for the welfare of our future patients with the same clinical course and presentation. The patient has no direct benefit from this study.

7. LIMITATIONS OF THE STUDY

One limitation of this study is that there is scarcity of existing research specifically focusing on this particular type of Parkinson's Disease in Asian individuals, which poses hurdles in obtaining comprehensive and diverse data for analysis and comparison. Additionally, another limitation is the high cost associated with genetic testing that serves as a crucial diagnostic procedure for this illness. The expense involved in accessing genetic testing limits the number of individuals who can undergo this diagnostic procedurein the Asian population, specifically in the Philippines, where financial constraints may further impede access to healthcare services.

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