Original Article

Familial Early-Onset Parkinsonism, Unique Features and Socioeconomic Impact- A Case Report with Literature Review

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ABSTRACT

Early-onset Parkinson's disease (EOPD) is rarer than the classical late-onset Parkinson's disease (LOPD). It refers to subjects with onset of symptoms between 21 and 40 or 50years of age. It progresses at a slower rate than LOPD, however has a greater impact on family, professional and social life as it occurs at the prime of life. A genetic aetiology is believed to be more common in EOPD than in LOPD. We present a 34year old right-handed primary school female teacher with onset of features of Parkinsonism at the age of 28years. There was family history of similar symptoms in father and paternal step-brother whose symptoms started in their early forties and early thirties respectfully. A correct diagnosis of EOPD is essential to aid management which usually involves a multi-disciplinary approach.

Keywords: Early-Onset, Family History, Genetics, Late-Onset, Parkinson's Disease, Social Impact

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disease that results from loss of neurons in the substantia nigra of the brain which are responsible for the secretion of dopamine. Typically, symptoms which characterise the disease include a resting tremor, bradykinesia, rigidity and postural instability.[1.2] Parkinson's disease (PD) rises in prevalence to about 2.6% in people aged 85 to 89 years.[3-5] The incidence rate of PD for age- and gender-adjusted cases is 13.4 cases per 100,000 individuals. The incidence rates differ for different age groups with a steady rise with increase in age group such as for those aged 30–39, 40–49, and 50–59, the incidence rates are 0.5, 2.5, and 9.8 cases per 100,000 individuals, respectively.[1,6,7] In Africa, crude prevalence rates of PD range from 7 to 43 per 100,000. 8 PD is classified based on age of onset of the disease as Early-onset PD (EOPD) and Late-onset PD (LOPD).[1,3] The EOPD has age of onset between 21and 40 or 50 years of age, with a subset below the age of 21years known as juvenile parkinsonism (JP). LOPD has age of onset above 50 years of age.[1,3,9,10]

EOPD is rarer than the classical late-onset Parkinson's disease (LOPD).[3.9.11] It accounts for 4-10% of all patients with Parkinson's disease (PD). 12 A genetic aetiology is believed to be more common in EOPD than in LOPD.[12-14] Patients with EOPD have an increased risk of genetic predisposition.[15,16] Although it has been reported that 6.9% of patients with LOPD have a family history of PD, the association of family history is higher in EOPD as 20% of patients with EOPD have a family history of PD. Furthermore, the age-specific risk of PD has been reported as 7.8-fold higher in relatives of

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patients with EOPD when compared with 2.9-fold among patients with LOPD.[15,17,14] Our patient had similar symptoms suggestive of EOPD in father and paternal brother. Genetic mutations associated with EOPD are most frequently located on parkin (PARK2), PINK1 (PARK 6), DJ-1 (PARK7), ATP13A2 (PARK9), and PLA2G6 (PARK14).[11,15] The first genome-wide assessment of Parkinson's disease genetics in African and African admixed populations identified a novel genetic risk factor GBA1 linked to the risk of Parkinson's disease in people of African ancestry.[18]

EOPD affects patients in the prime of their life, hence has an extraordinary impact on their family, social, and professional life. It typically progresses at a slower rate than LOPD hence there is a tendency to a longer survival. Individuals with EOPD are more prone to develop levodopa-related motor complications, including dyskinesia. A correct diagnosis is essential to aid management which usually involves a multi-disciplinary approach.[1,3,11] We present a case of a 34-year female with familial history of EOPD. The unique presenting features of EOPD and socioeconomic impact in a resource poor centre will be discussed here.

CASE REPORT

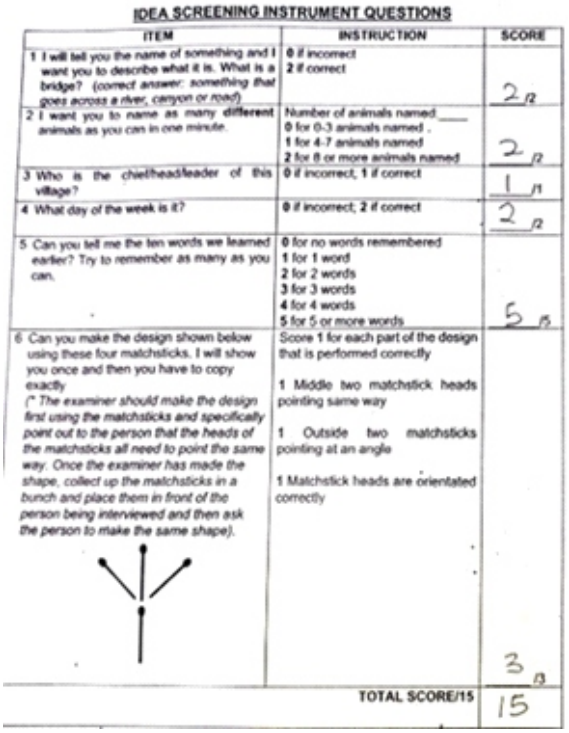
We report a case of a 34-year- old female Primary school teacher who presented with bradykinesia, bilateral resting tremors with rigidity of both upper limbs, painful muscular contractions of both lower limbs with some level of paraparesis, reduced voice volume, drooling of saliva, and small handwriting of greater than 5years duration. Tremors of the right hand was noticed as the initial symptom. Contractions in both lower limbs resulted in difficulty walking with poor balance and associated fear of falling. There is history of such symptoms in father and paternal step-brother. Father's symptoms were said to have begun in his mid- forties, while brother's symptoms started in his early thirties. Her symptoms started at the age of 28years. Father had been on Artane for years prior to his demise from complications following a fall. Elder brother had been on Artane but currently on treatment for Parkinson's disease. There is significant smoking history in mother even while pregnant with index patient and she was diagnosed with severe growth restriction in-utero, however she was delivered at term with very low birth weight. She had been self-medicating on Artane and herbal preparations. She presented on account that she was informed her elder brother was receiving treatment at a tertiary hospital at another state and was almost normal without any signs of the disease. Furthermore, she has not been in a relationship for over 2 years and had stopped working for about a year due to severity of her symptoms.

Examination revealed a young lady, anxious looking with a spastic unsteady gait. There was hypomimia with mild loss of speech volume, however speech was clear and easy to follow. She had resting tremors of both hands, with significant rigidity in both arms, legs and neck. There was marked reduction in finger and toe tapping, rapid alternating hand movements and leg agility. She had some difficulty arising from a chair. She scored 30/40 on the Movement Disorder Society- Unified Parkinson's Disease Rating Scale (MDS- UPDRS).[19] Her score on the Montreal Cognitive Assessment instrument (MoCA)[20] was 28/30 (cut off for normal being 26). Total score on Identification and Intervention for Dementia in Elderly Africans (IDEA)[21] Screening instrument was 15/15 in 6 minutes (figure 1), while her Parkinson's disease quality of life Questionnaire (PDQ 8)[22] score was 18/32 (56.25%), figure 2.

Blood investigations for full blood count, electrolyte, urea creatinine, liver function test and urinalysis were essentially normal. Brain Computerised Tomography scan was normal. Magnetic Resonance Imaging were ordered for the brain and whole spine, but were not done due to financial constraints as she has not been working due to her clinical condition.

A working diagnosis of suspected EOPD (to keep in view atypical parkinsonism) was made mainly based on family history and clinical features. She was commenced on a Levodopa challenge of 250mg per day in 2 divided doses and physiotherapy. On a 2-week follow up, patient was noticed to have significantly improved especially in tremors, gait and rigidity and could now cover a distance of over 500m on foot without stopping to rest as against a

previous 100m. She described her improvement as "miraculous". Her score then on the UPDRS was 19. At 4 weeks on levodopa, her symptoms were minimal and she could cover a distance of greater than 1Km on foot. Furthermore, there was improvement in the muscle contractions she experienced previously. She was able to return to her teaching job.



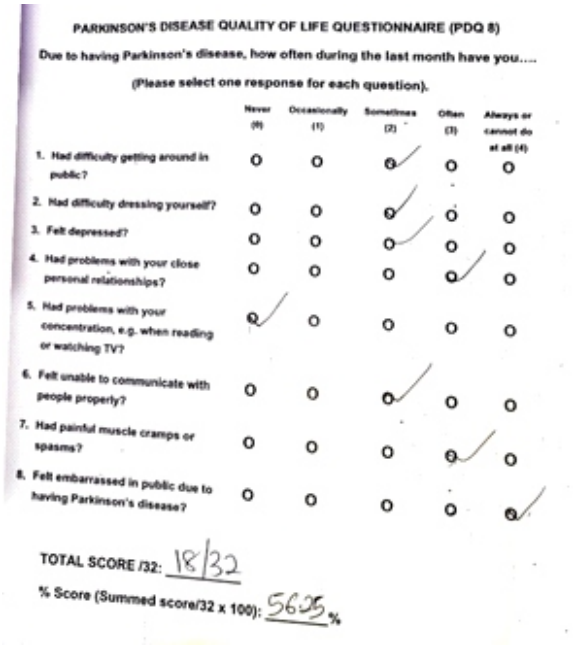
IDEA SCREENING INSTRUMENT QUESTIONS

ITEM	INSTRUCTION	SCORE
1 I will tell you the name of something and I want you to describe what it is. What is a bridge? (*correct answer: something that goes across a river, canyon or road*)	0 if incorrect 2 if correct	2/2
2 I want you to name as many different animals as you can in one minute.	Number of animals named ____ 0 for 0-3 animals named . 1 for 4-7 animals named 2 for 8 or more animals named	2/2
3 Who is the chiefheadfleader of this village?	0 if incorrect; 1 if correct	1/1
4 What day of the week is it?	0 if incorrect; 2 if correct	2/2
5 Can you tell me the ten words we learned earlier? Try to remember as many as you can.	0 for no words remembered 1 for 1 word 2 for 2 words 3 for 3 words 4 for 4 words 5 for 5 or more words	5/5
6 Can you make the design shown below using these four matchsticks. I will show you once and then you have to copy exactly (** The examiner should make the design first using the matchsticks and specifically point out to the person that the heads of the matchsticks all need to point the same way. Once the examiner has made the shape, collect up the matchsticks in a bunch and place them in front of the person being interviewed and then ask the person to make the same shape).*	Score 1 for each part of the design that is performed correctly 1 Middle two matchstick heads pointing same way 1 Outside two matchsticks pointing at an angle 1 Matchstick heads are orientated correctly	3/3
	TOTAL SCORE/15	15

Figure 1. Patient's performance on the IDEA screening instrument

DISCUSSION

In a resource-poor setting where investigations are limited and genetic testing almost non-existent, a high degree of suspicion coupled with a Levodopa-challenge test is required to make a diagnosis of EOPD. Some patients with EOPD remain undiagnosed due to possible unfamiliarity of some clinicians especially non-neurologists with the condition mainly on account of the age of onset and atypical presentation of PD. Some patients with EOPD tend to go for alternative forms of management when their conditions do not improve despite visiting a number of physicians or might self-medicate based on contact with persons with similar conditions such as was the case in our index patient.



PARKINSON'S DISEASE QUALITY OF LIFE QUESTIONNAIRE (PDQ 8)

Due to having Parkinson's disease, how often during the last month have you....

(Please select one response for each question).

	Never (0)	Occasionally (1)	Sometimes (2)	Often (3)	Always or cannot do at all (4)
1. Had difficulty getting around in public?	O	O	✓	O	O
2. Had difficulty dressing yourself?	O	O	✓	O	O
3. Felt depressed?	O	O	O	✓	O
4. Had problems with your close personal relationships?	O	O	O	O	✓
5. Had problems with your concentration, e.g. when reading or watching TV?	✓	O	O	O	O
6. Felt unable to communicate with people properly?	O	O	✓	O	O
7. Had painful muscle cramps or spasms?	O	O	O	✓	O
8. Felt embarrassed in public due to having Parkinson's disease?	O	O	O	O	✓

TOTAL SCORE /32: 18/32

% Score (Summed score/32 x 100): 5625 %

Figure 2. Patient's performance on the PDQ8

As such, patients with EOPD tend to present later from time of onset of symptoms than patients with the typical EOPD.

Clinical features of EOPD

EOPD is rarer than the classical late-onset Parkinson's disease (LOPD) with age of onset between 21-40 or 50 years.[1,3,9-11] Our patient was 28 years at onset of symptoms. Patients with EOPD may present with atypical symptoms such as dystonia and pyramidal signs, however they generally present with bradykinesia, tremors and rigidity.[23,24] There are reports of improvements in symptoms with sleep in some patients with EOPD.[9] Rigidity is reported as the predominant initial motor symptom more frequently seen in patients with EOPD unlike the LOPD where gait instability is the most likely initial symptom.[17] Frequency of tremor or bradykinesia has not consistent in reported literature as some have reported an increased frequency while others a decreased frequency.[15] One study reported no significant difference.[25]

Dystonia is more common in EOPD in the early stages than in LOPD where it is more in the late stages. In LOPD, dystonia usually occurs as a disease-related motor feature or as part of levodopa-induced dyskinesias. In contrast, in drug-naïve

EOPD, dystonia is very common, occurring as an early co-existing and occasionally presenting feature.[3,26] In a study of 358 patients, dystonia was found to be a more frequent presenting symptom in EOPD than LOPD. Within 2 years of onset, an additional 11% of EOPD and 1% of LOPD developed dystonia.[15,25] The dystonia in EOPD has been described as a mobile dystonia affecting all body parts, with the foot or leg being more commonly involved.[3]

Levodopa- induced dyskinesias have been described to occur more frequently in EOPD than in LOPD.[3,15,17,25] It is not yet understood why levodopa-induced dyskinesia are more common in patients with EOPD, however it may be attributable to the greater tendency to exhibit maladaptive responses in these patients.[3,27] Another reason might be that the higher synaptic dopamine turnover reported in patients with EOPD compared to patients with LOPD may result in large swing in dopamine synaptic levels which possibly contribute to levodopa-induced dyskinesia.[28]

Non-motor symptoms of PD such as depression and anxiety are frequent among patients with EOPD.[10,23,29] Unlike the LOPD with studies demonstrating cognitive impairment even amongst Africans,[30,31] EOPD has been reported to have a low incidence of cognitive impairment. In a study, EOPD was found to have a higher rate of depression, worse emotional well-being, and poorer quality of life.[10,23,29,32]

Socioeconomic impact of EOPD

Patients with EOPD may face challenges getting into relationships or maintaining previous relationships due to the strain of a chronic illness.[15] In comparison with patients with LOPD, patients with EOPD tend to have different family and societal engagements. These include most persons with EOPD having a job whereas those with LOPD may be retired. Also, people with EOPD may have young children or may want to start a family.[3] Our patient desired to get into a meaningful relationship with marriage as the goal and possibly have children.

It had been reported that 55% of patients with EOPD retire early or within 10years of disease onset.[11] Our patient had given up her teaching job due to her illness but with treatment was able to return back to work.

Management of EOPD

Management of EOPD is multi-disciplinary. It involves the use of Levodopa to relieve the motor symptoms of the disease just as in LOPD. Alternatively, dopaminergic therapy with dopamine agents may be used. Management of EOPD should encompass Neurologists, physiotherapists, occupation therapists and psychiatrists in view of anxiety and psychosocial problems which such patients usually experience. Care should be tailored to individual needs.

CONCLUSION

EOPD is a rare form of PD with significant socio-economic impact in patients who are usually at the prime of their life. It's associated with challenges in diagnosis and management. EOPD has more genetic and hence familial associations than the typical LOPD. More studies like the on-going genomic study in Nigeria need to be carried out to improve the prospects of this complex disease.

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