JOURNAL OF NEUROLOGY AND PSYCHOLOGY RESEARCH

CASE REPORT Open Access

Distinctive Phenotype and Treatment Response of a Novel PARK7 Variant

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Received date: September 18, 2023, **Accepted date:** September 29, 2023, **Published date:** November 03, 2023.

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Abstract

In this paper, we present a case of early Parkinson's disease with atypical clinical manifestations and a novel genetic variant. This variant appears to be unresponsive to current Parkinson's medications and may have a more unfavourable clinical course. Our objective in sharing this case is to increase awareness of new genetic variants that may have unique clinical features and to identify additional cases worldwide to establish the pathogenicity of this variant and improve our understanding of this variant in Parkinson's disease.

Introduction

Parkinson's disease (PD) is a progressive neurological disorder characterised by a large number of motor and non-motor features. It is considered one of the most common neurodegenerative disorders with an estimated prevalence 2% of people above the age of 60 and 4% above the age of 80 years are affected worldwide.(1) Saudi Arabia statistics community survey was conducted on 1993 found that 0.27 out of every 1,000 people in Thuqbah, Saudi Arabia had Parkinson's disease.(2) Historically, it was first described by James Parkinson in 1817. More than 100 years (1919) before it was recognised that patients with PD lose cells in the substantia nigra (3). Over the last two decades there has been expansion in hereditary Parkinson's disease; a large number of additional genes have been described as monogenic causes for PD11. There are specific genes well known as parkin (PARK2), PINK1 (PARK6), or DJ-1 (PARK7) 7. Over the past 10 years multiple novel causative genes that cause dominant Parkinson's disease

were reported for the first time like (DNAJC13, CHCHD2, TMEM230, SYNJ1, DNAJC6, VPS13C, and PTRHD1) (4). Some genes are associated with specific clinical syndromes with some variability in clinical manifestations.

Methods

An adult lady with atypical presentation of Parkinson's disease following in the Neurology department of King Abdulaziz Medical City, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia, from August 2016 until 2023.

Case Presentation

A 38-year-old woman had been experiencing tremors for 13 years, beginning at age of 26. At first, the tremors were asymmetrical and primarily affected her arm movements, inconsistently worsening with stress and during daily activities but not related to specific tasks. The patient had no significant past medical or surgical history and no family history of neurological disease and was not taking any medications. Her clinical examination was remarkable for left arm tremor pronounced by action; otherwise, she had non-focal cranial nerve, motor, sensory and cerebellar examination. Routine basic blood work up was all within normal limits. Non enhanced Brain MRI unremarkable for structural abnormality. Initial diagnosis was essential tremor and treated with propranolol. However, her symptoms were not resolved totally and worsened over the next 2 years. At that time, her examination was alarming for an increase in tremor frequency on the left side, and for the first time noticed at rest. Moreover, subtle rigidity on the same side.

Two months later, her examination was remarkable for increased rigidity, mild slowness in the left arm and her tremor not any more responsive to propranolol. These findings suggested early-onset Parkinson's disease. A trial of Sinemet started and extensively investigated through repeated brain MRI and Wilson's disease workup in addition to other blood work up were unremarkable. After starting the Sinemet she developed facial dyskinesia with no significant improvement achieved. Trihexyphenidyl started for 6 months but she was complaining of worsening in her condition. Follow up Clinical assessment was remarkable for loss of facial expression on both sides of the face, decreased eye blinking, slowed up saccad with limited vertical gaze. Slow understanding speech, with intact cognition. Significant left side rigidity, resting tremor right more than left with newly frequent episodes of myoclonus. Cranial nerves were normal, with no pyramidal symptoms or abnormal cerebellar findings. Pramipexole started and titrated up slowly, with mild improvement in her symptoms achieved after 2 months of starting the medication.

We performed a Genetic test that was remarkable for homozygous PARK,7 genes with new variants coordinates C.191_192del and amino acid changes P. (Glut64 Glyphs*4). This new variant has never been described before.

Discussion

Parkinson's disease is considered as a common neurodegenerative disorder around the world. (15) Has been studied extensively over the past century and identified in terms of typical and atypical clinical presentation. And understood the commonest cause is idiopathic, with high prevalence at the age of 60 and 70(16). In the last two decades hereditary Parkinson's disease has been identified, and since then, a large number of new genotypes have been discovered in various families around the world. High-throughput techniques such as exome sequencing will also reveal new genetic causes in the near future. The genotype influenced the phenotype and several genes have been linked by solid evidence from observations of mutation co-segregation into clinically similar disease subtypes

in multiple families with Parkinson's disease.

The clinical value of knowing the genotype and linking it to the usual clinical presentation; includes facilitating clinical diagnosis, recognizing the most effective class of medical therapy, or trying surgical options like Deep brain stimulation. On other hand, establishing family counselling, and enabling multilevel interventions aiming to apply primary prevention.

The usual presentation in patients with parkin mutations tended to have earlier and more symmetrical onset, slower progression of the disease, and greater response to levodopa despite lower doses. In our case, we have new variant coordinates in PARK 7 whose expression is different manifestations of other PARK7 variants starting from very early onset, a progressive course and tremor as early predominant features, other new features include myoclonus and limited vertical vision. And absences of other PARK gene variants manifestations like visual hallucination and dementia and pyramidal signs (17). Compared with the treatment response, it appears to have low responsiveness to most PD treatment agents and have more complications from treatment, such as dyskinesias and fluctuation of symptoms.

Conclusion

Hereditary Parkinson's disease has numerous genotypes with new variants that are expected to increase in number with the availability of advanced techniques such as exome sequencing. It is clear that genotype plays a role in the phenotype of Parkinson's disease. However, sharing atypical cases is necessary to establish the pathogenicity of new variants.

Parkinson's disease (PD) is a common neurodegenerative disorder that can be caused by a variety of genetic factors. Genetic testing for PD can be helpful for confirming a diagnosis, identifying the specific gene that is mutated, and screening family members of people with PD. Patients with PARK7 mutations more often have an earlier onset of PD, with variety in clinical presentation. Specifically, tremor, myoclonus, and limited vertical vision. They are also likely to experience visual hallucinations, dementia, and pyramidal signs, (5) though overall have a benign course and quite good response to treatment in comparison to a more progressive course, and a different pattern of symptoms than patients with mutations in other genes.

Our patients with new variant PARK7 mutations appear to have a less favourable response to most PD treatment agents, and a higher risk of experiencing complications from treatment, such as dyskinesias and fluctuation of symptoms and clinically has a complex picture. It is clear that genotype plays a role in the phenotype of Parkinson's disease. Hereditary Parkinson's disease has numerous genotypes and new variants that are expected to increase in number with the availability of advanced techniques such as exome sequencing. For that, sharing atypical cases is necessary to establish the pathogenicity of new variants.

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