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Clinical Observations

Early-Onset Parkinsonism: Case Report and Review of the Literature

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ABSTRACT

BACKGROUND: Early-onset parkinsonism can be caused by PTEN-induced putative kinase 1 (*PINK1*) gene defects and is usually characterized by an age of onset in the fourth decade of life, slow disease progression, resting tremor, rigidity, bradykinesia, postural instability, and levodopa-induced dyskinesia. **METHODS:** We evaluated a child with early-onset symptoms and performed a literature review for previously reported examples of children aged 18 years or less with *PINK1* gene defects. **RESULTS:** We describe a five-year-old boy with autosomal recessive early-onset parkinsonism caused by a homozygous missense mutation in the *PINK1* gene. This is the youngest individual yet reported with early-onset parkinsonism. **CONCLUSION:** PINK1-type of early-onset parkinsonism can occur in very young patients, and phenotypic expression of *PINK1* mutations may depend on age of onset and ethnicity.

Keywords: pink1, early-onset parkinsonism, Parkinson disease, parkinsonism, dystonia, movement disorders

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Introduction

Parkinsonism is a neurodegenerative disorder often of unclear etiology and characterized by bradykinesia, rigidity, resting tremor, and postural instability. Several genes for early-onset parkinsonism (EOP) have been identified. These include *Parkin* at PARK2[1] (OMIM#602544), *PINK1* at PARK6[2] (OMIM#608309), *DJ-1* at PARK7[3] (OMIM#606324), *ATP 13A2* at PARK9[4] (OMIM#610513), *PLA2G6*at PARK14[5] (OMIM#603604), *FBXO7* at PARK15[6] (OMIM#260300), and *SYNJ1*[7] at PARK20 (OMIM#604297). Of these, only the first three forms present with classical parkinsonism, albeit with an earlier mean age of onset than idiopathic Parkinson disease (PD).[8,9] About half of the individuals who are diagnosed with familial parkinsonism with autosomal inheritance who present before age 45 years are caused by mutations in the *Parkin* gene.[10] Seemingly sporadic cases with mutations in the same gene account for about 15% of patients with early-onset disease.[10] The PTEN-induced putative kinase 1 (*PINK1*) gene is the second most common cause of EOP,[11] with mutations representing approximately 4% to 5% of autosomal recessive patients and 1% to 2% of sporadic individuals with early onset.[12] Overall, EOP has a better response to levodopa and a slower disease course.[8]

Additional features of early-onset classical parkinsonism include dystonia, hyperreflexia, abnormal behavior and/or psychiatric manifestations, and dyskinesias as a result of treatment with levodopa.[13] The age of onset is highly heterogeneous even among individuals with the same mutation. Nevertheless, the most common age of onset is between 30 and 40 years.[12-14]

We describe five-year-old boy diagnosed with autosomal recessive EOP caused by a homozygous missense mutation in the *PINK1* gene. This is the youngest individual yet reported with a mutation in this gene. We further

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review the literature regarding the clinical and molecular findings of parkinsonism in children.

Methods

After providing informed consent, the patient underwent a standardized neurological examination by a neurologist and a geneticist. The diagnosis of PD was based on the clinical evaluation in addition to whole exome sequencing. Moreover, the whole exome sequencing data were specifically reviewed for the presence of *SLC6A3*, *TH*, or *GCHI* mutations, all of which were absent and properly covered by the exome sequencing (for detailed methods of whole exome sequencing, the variant filtering strategy, and median coverage of the sequenced sample, please see supplementary materials).

Literature review

We searched the Medline database from the first description of the *PINK1* gene in 2006 to September 2014. The search terms *PINK1* and *PARK6* yielded 527 publications. After excluding reviews, duplicate publications of cases without additional information, and articles lacking clinical information or *PINK1* mutation status and limiting the age to 18 years or less, six articles describing a total of 15 patients were evaluated (Table).

Results

Patient description

This five-year-old Pakistani boy was born to healthy first-degree cousins after an uneventful pregnancy and delivery. He had a healthy three-year-old sister. The proband developed normally until age four years when he started to exhibit bilateral resting tremor and slurring of speech. He held both his hands in an unusual posture with both fists closed but was able to open them immediately on command. The child also showed severe gait impairment accompanied by frequent daily falls. Subsequently, he developed upper limb dystonia.

Most of the time, he is bedridden (Fig 1 and Video 1); he kept his head tilted to one side while walking in a dystonic manner. In addition, he developed constipation and social anxiety. On examination, his height was 95 cm (10th to 25th percentile), weight was 14 kg (10th to 25th percentile), and head circumference was 49 cm (25th percentile). Neurological examination showed tremor in both hands along with upper limb dystonia and a staggering gait. Reflexes were normal and there was no

TABLE.
Age of Onset, Clinical and Molecular Findings of Previously Reported Patients Aged ≤18 Years With Early-Onset Parkinsonism Caused by a Mutation in the *PINK1* Gene

Author, Year	Number of Cases	Male:Female Ratio	Ethnicity	Age of Onset	Clinical Features	Molecular Findings
Hatano Y et al., 2004[15]	1	0:2	Taiwanese	18	Resting tremor, rigidity, bradykinesia, postural instability, levodopa-induced dyskinesia, slow progression	Compound-heterozygous mutation: (p.Q239X/R492X)
Rohé CF et al., 2004[16]	1	F	Italian	9	Fear, claustrophobia, and a feeling of derealization resolved after 1 year. At age 25 years, patients started to show tremor, rigidity, marked diurnal fluctuations with amelioration after nocturnal sleep, bradykinesia, excellent initial response to L-dopa, slow progression, and levodopa-induced dyskinesia	Homozygous frameshift mutation 1573_1574 insTTAG
Leutenegger AL et al., 2006[17]	8	2:6	Sudanese	9-14	Bradykinesia at onset, rigidity, resting tremor, dystonia at onset, improvement with levodopa, diurnal fluctuation, slow progression, presence of a striatal toe on the plantar reflex in two patients, absence of other atypical neurological signs (e.g., dementia or hallucinations, dysautonomia, pyramidal signs, or ophthalmoplegia)	Homozygous missense mutation (p.A217D)
Weng YH et al., 2007[18]	2	0:2	Taiwanese	17-18	Resting tremor, dystonia at onset improvement with levodopa, diurnal fluctuation, slow progression	Compound-heterozygous mutations (p.Q239X/R492X)
Kumazawa R et al., 2008[19]	1	0:1	Greek	10	Resting tremor, rigidity, bradykinesia, shuffling gait, postural instability, levodopa-induced dyskinesia	Homozygous deletion: c.889delG [p. Asp 297MfsX22]
Cazeneuve C et al., 2009[20]	2	2:0	Sudanese	11, 15	Bradykinesia at onset, rigidity, resting tremor, improvement with levodopa, slow progression, levodopa-induced dyskinesia	Homozygous deletion in exons 4 to 8