A Case of Gillespie Syndrome without Aniridia

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Abstract

Gillespie syndrome is a rare, congenital disease that typically presents in childhood with cerebellar ataxia, aniridia, and intellectual disability. Since the first case was reported in the literature in 1965, recent studies have shown that the mutations in Gillespie patients occur in the 1,4,5-trisphosphate receptor type 1 (ITPR1) gene. In our study, we present the first case of genetically diagnosed Gillespie syndrome in a child who does not present with aniridia. This child of first-degree consanguineous parents presents with a novel homozygous mutation in the ITPR1 gene. In addition, her other symptoms are mild when compared to known Gillespie syndrome cases in the literature, and this is the first reported case of Gillespie syndrome in Lebanon and the Middle East. This underscores the importance of genetic testing when diagnosing neurological syndromes, and the potential for multivariable presentation of patients with such syndromes.

Keywords: Gillespie syndrome; Aniridia

Introduction

Cerebellar ataxia and intellectual disability can present in childhood due to many etiologies, several of which are genetic. Gillespie syndrome (GS, MIM: 206700), also known as aniridia-cerebellar ataxia-intellectual disability syndrome, is a rare, congenital disease characterized by a range of neurological findings including partial aniridia, non-progressive cerebellar ataxia and intellectual disability [1]. It is described as a monogenic condition with mutations in the inositol 1,4,5-trisphosphate receptor type 1 (ITPR1) gene being the causal factor. Previous reports describe the pattern of inheritance of the disease as autosomal dominant or recessive [2].

There are 3 ITPR genes in the human genome, and their resulting monomeric conformations form Ca2+ channels primarily in the intracellular membranes of Ca2+ stores. IP3 responds to various extracellular signals to diffuse through the cytosol and bind to the IP3 receptor which is formed by the 3 ITPR genes including ITPR1 [3].
Ca2+ channel activity is central to many cellular functions, including proliferation, secretion, division, contraction, and apoptosis. Studies have shown that abnormal intracellular Ca2+ signaling can cause spinocerebellar ataxia in human and mouse models [4]. This connects genetic mutations in the ITPR1 gene to the presentation of Gillespie syndrome patients with congenital ataxia. Gillespie syndrome was first described in 1965 [5] and since then, approximately 30 cases were reported in the literature by 2020 [6,7]. To the best of our knowledge, we are presenting the first case of Gillespie syndrome with absence of aniridia. This is also the first reported case of Gillespie in Lebanon and the Middle East.

Case Presentation

The proband is a 9-year-old Lebanese girl born to healthy first-degree consanguineous parents who previously had 5 healthy sons. She was delivered at the hospital by a normal, uncomplicated vaginal delivery with a birth weight of 3000g and a head circumference of 35 cm. The patient presented to our clinic for poor balance, noted when she first started walking at 17 months. She also had intermittent left eye deviation notable since the age of 21 months and ataxia identified at the age 3 years.

Neonatal history was unremarkable; her neurological history was significant for mild motor delay, dyslexia and school difficulties. She was also hospitalized once for gastroenteritis at the age of 2 years. For better evaluation, whole exome genetic testing was performed and showed a homozygous mutation in the ITPR1 gene located on the chromosome 3p26.1 (1:c.2T>A) leading to a change in the translation initiation site of the ITPR1 gene. A diagnosis of Gillespie syndrome was subsequently made.

On physical examination aged 9 years, the patient was conscious, alert and cooperative. Her pupils were symmetric and reactive to light and she had mild and intermittent left external eye deviation. Her head circumference was of 55 cm. Neurological examination revealed ataxia with wide gait but intact proprioception. She also displayed intentional tremor in both upper extremities, but her deep tendon reflexes were present and symmetric. A magnetic resonance imaging (MRI) of the brain was within normal limits.

Discussion

A diagnosis of Gillespie syndrome is typically associated with aniridia. Classic aniridia (OMIM 106210) is a rare congenital condition with panocular involvement, consisting of partial or complete absence of the iris. However, aniridia could be a feature of other systemic conditions like Gillespie syndrome and WAGR syndrome (Wilms' tumor, aniridia, genitourinary anomalies, mental retardation) [8].

Bilateral iris hypoplasia or bilateral partial aniridia has been reported persistently in Gillespie syndrome cases, making it one of the earliest symptoms in the course of the disease. The iris typically has a unique “scalloped” appearance at the inner pupillary edge due to aplasia of the sphincter pupillae [9].

Our case is the first case of Gillespie reported in the literature with absence of aniridia. The ocular findings were limited to external left eye deviation. Genomic studies were required to arrive at the diagnosis, and this suggests that many syndromes can be misdiagnosed without genetic analysis. This critical finding indicates that Gillespie syndrome should not be ruled out due to absence of aniridia.
In fact, many of her symptoms were milder in presentation compared with other Gillespie cases. It may be that her newly described mutation in the ITPR1 gene confers a mild form of Gillespie syndrome. This may also play a role in the absence of aniridia. Another major finding in Gillespie is cerebellar involvement which usually presents as hypotonia and delayed motor developmental milestones early in life. Our patient started walking at 17 months, which is earlier than most reported cases [6]. Ataxia and poor balance were also noted despite her brain MRI showing no cerebellar atrophy which is another particular finding in our case. However, a possible cerebellar atrophy in the future cannot be ruled out as some have reported progression to atrophy in adulthood [10].

Genetic testing is necessary to make a definitive diagnosis of Gillespie and mutations in the ITPR1 gene on chromosome 3p26 are the only ones reported so far for this condition. The ITPR1 receptor plays a role in Ca2+ release from the endoplasmic reticulum and has been linked to play an important role in cerebellar functions. Without genetic testing, we could not have diagnosed our patient with Gillespie syndrome due to the absence of some cardinal findings.

Table 1: Case description of patients with confirmed Gillespie syndrome from 2019 onwards.
M: male; F: female; y: year; m: month; N: no; Y: yes; NR: not reported.

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<tbody>
<tr>
<td>Sex</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>F</td>
</tr>
<tr>
<td>Age at Presentation</td>
<td>NR</td>
<td>1y 8 m</td>
<td>23y</td>
<td>9y</td>
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<tr>
<td>Bilateral partial aniridia</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>N</td>
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<tr>
<td>Pupils reactive to light</td>
<td>N</td>
<td>Y (reduced)</td>
<td>NR</td>
<td>Y</td>
</tr>
<tr>
<td>Other ophthalmic findings</td>
<td>Dilated pupils, bilateral ptosis, mild visual impairment</td>
<td>Lack of gaze fixation, pale optic nerve, unformed macula, no convergence</td>
<td>Nystagmus</td>
<td>Left external eye deviation</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>N</td>
<td>Y (severe)</td>
<td>Y</td>
<td>Y (mild)</td>
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<tr>
<td>Motor Findings</td>
<td>Intention tremor</td>
<td>Dysmetria</td>
<td>Dysarthria</td>
<td>Intentional tremor</td>
</tr>
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Deep Tendon Reflexes | Brisk | Normal | NR | Normal
---|---|---|---|---
Age at Walking | 2.5 y | NA (1y 8 m) | NR | 1.4y
Ataxia | Y (Mild) | Y | Y | Y
Cerebellar findings on MRI | Atrophy of Cerebellar Vermis (26y) | Mild Cerebellar Atrophy and Deepened Sylvian furrows | Mild Cerebellar Atrophy | N (9y)
Intellectual disability | N | Y | Y | ?

**Conclusion**

Gillespie syndrome is a rare congenital disorder with a diagnosis usually based on partial aniridia and cerebellar ataxia findings and genetic testing revealing mutations in the ITPR1 gene.

We report a case of Gillespie syndrome that appears milder than previous presentations of the disease. It is also the first report of Gillespie without aniridia. Genetic testing is crucial in diagnosing such diseases as clinical findings can sometimes appear milder or can be non-existent like in our case.

**REFERENCES**

