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Case Report

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# A Case of Autosomal Recessive Dopa Responsive Dystonia (DRD) with GCH1 Gene Mutation

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## Abstract

*Timely diagnosis of Segway's disease is very important and neurologists should always consider it in the differential diagnosis of dystonia. Because the symptoms of this disease can be resolved with low doses of Levodopa and the patient can lead a normal life in the community. Another important issue is genetic counselling for these patients before marriage or pregnancy, the mode of inheritance and the risk of their children should be investigated and estimated. Here we present a case of Segawa patient who was challenging in genetic counselling.*

## 1. Introduction

Diagnosing Segway's disease or DRD as early as possible is very important because these patients often respond well to low doses of Levodopa and can live a normal life. In general, in every patient, especially children and adolescents who are present with dystonia, this disease should be considered, Levodopa treatment should be tried, and genetic testing should be requested to confirm the diagnosis and advice for the patient who wants to become pregnant.

In 1976, Segawa et al. Reported a case of childhood-onset dystonia called "hereditary progressive dystonia with diurnal fluctuations" that responded well to low-dose levodopa [1]. In 1988, Nygaard et al. They proposed the title "Dystonia with good bipedal response" (DRD) for this disease [2].

Segawa syndrome is a very rare genetic disorder characterized by an unbalanced or clumsy gait (abnormal gait) and dystonia. Dystonia is a general term for a group of muscle disorders that usually show themselves with involuntary contractions in some muscles. These involuntary contractions involve the body in abnormal and sometimes painful movements and positions. Dystonia in Segawa syndrome usually affects the legs, but some children may first develop dystonia in the upper limbs. In some cases, usually in teenagers and adults, the symptoms of Segawa syndrome may be worse or more severe in the afternoon and evening than in the morning (diurnal fluctuations of symptoms). Symptoms of Segawa syndrome usually become apparent around the age of six, although cases with onset in adolescence and even adulthood have been reported. No reduction in IQ has been reported [3,4]. Children with Segawa syndrome usually show significant and sustained improvement when treated with levodopa. Women are affected 2 to 4 times more often than men.

## 2. Case Report

The patient was a 17-year-old girl who came to our hospital with a complaint of difficult walking. The patient's problem started 4 years before the visit, when she noticed some weakness on the left side of the body and walked on the toe of the left foot. This difficulty in walking worsened especially at night. The patient also had a deviation of the neck to the left side. He was also complaining of back and hip pain and was delayed in walking as a child. The patient had referred to a neurologist and neurosurgeon but she was diagnosed with cerebral palsy (CP) accompanied by seizures, so was treated with Botox and anticonvulsant drugs which did not work.

In the examination of the patient, her mental condition was normal. Pupils were normal in size and reactive. All cranial nerves examinations were normal. The muscle tone of the right limbs increased. The distal and proximal force of the upper and lower limbs was normal. The plantar flexion force of the left leg was normal, but there was limitation in dorsiflexion of the left leg. The patient's tendon reflexes were +3 and the plantar reflex was flexor bilaterally. The patient had an increase in the plantar arch on both sides. Cerebellar examinations were normal, but the patient walked on the toe of the left foot. Romberg test was also negative. The patient did not report a family history of a similar disease. The patient was treated with 200 mg Sodium Valproate - 25 mg. Baclofen and 2 mg of Bipyridine per day.

There were no pathological findings in patient's brain MRI and laboratory tests were normal.

The patient was diagnosed with seaway's disease, and Levodopa was prescribed at a dose of 55 mg daily. It was prescribed twice

a day and it was recommended to visit again to check the clinical response in the next 10 days. When the patient returned in the next ten days, all the patient's symptoms had improved dramatically and the diagnosis of dystonia responding to Levodopa (DRD) was confirmed. Sodium valproate and baclofen were gradually discontinued. The patient had no symptoms 6 months later and did not have a visit for three years until his marriage when he is planning to get pregnant and is worried about transferring the disease to his child.

The patient was informed that this disease can have an autosomal dominant transmission, and in this case it can be transmitted to children at a rate of 50%. Therefore, a genetic analysis was recommended and it was determined that the patient has a homozygous CGH1 c.175C>G mutation. The genetic test details were as:

DNA Sample from the case was investigated for GCH1 gene (full gene, all exons and exon- intron boundaries) by PCR -Sequencing method.
A reported homozygous mutation as c.175 C>G (p R59G) was detected.
Gene: GCH1
DNA Changes: c.175C>G p.R59G
Zygodity: Homozygous
Clinical Significance: Pathologic (Kim et al, 2008)

After the genetic analysis was determined, a more detailed family history was taken. The patient's parents were cousins and did not have any symptoms of muscle and movement disorders. Our conclusion was that the patient probably inherited each gene from one of his parents.

## 3. Discussion

Unfortunately, like our patient, for most of the cases in which movement symptoms appear at a young age, the diagnosis of cerebral palsy is first made, and they may receive symptomatic treatment for a long time with this diagnosis and be deprived of effective and specific treatment [5,6].

Currently, based on clinical and laboratory reports, three types of Segawa syndrome have been identified. The first type which is called DYT5a, is due to mutations in the GTP cyclopyrrolones 1 (GCH1) gene (14q22.1 to q22.2) which encodes an enzyme needed for the biosynthesis of tetrahydrobiopterin, the important co-factor for tyrosine hydroxylase. The second type named DYT5b and is caused by mutations in the tyrosine hydroxylase TH gene (11p15.5) encoding tyrosine hydroxylase, the essential enzyme for catalysing the conversion of tyrosine to L-dopa, the precursor of dopamine. Third type is DRD due to an SRD which is due to mutations in the SPR gene (2p14-p12), that encodes the enzyme sepiapterin reductase (SR), which is also required for the biosynthesis of tetrahydrobiopterin [7,8].

Most of the existing articles have reported that mutation in GCH1 gene results to an autosomal dominant phenotype. In our patient, the parents did not have any symptoms, while the patient was homozygous and had acquired both genes from his parents.

As a result, if the patient's spouse genetically lacks the DRD gene, there is a 50% chance that half of their children will have the disease gene, but they will probably not show symptoms of dystonia like the patient's parents. Unfortunately, we were not able to examine the patient's parents genetically, but the homozygous status of the patient's genotype, the absence of related symptoms and complaints, and their complete health in repeated clinical examinations, are interpreted in favour of the definite healthy carrier of the parents and the 50% probability of the patient's children becoming healthy carriers. However, genetic testing of the patient's husband before pregnancy, prenatal testing, and pre-implantation genetic testing were recommended.

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