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CORRECT DIAGNOSIS CHANGES CHILD'S LIFE: CASE REPORT OF DOPA-RESPONSIVE DYSTONIA (DRD)

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ABSTRACT
Dopa-responsive dystonia (DRD) classically presents as limb-onset, diurnally fluctuating dystonia that has a clear and sustained response to levodopa. The most common cause is mutation in the GTP cyclohydrolase I gene (GCH1). However, due to the heterogeneity of conditions that underlie DRD, it is frequently misdiagnosed, which delays the appropriate treatment with Levodopa. In this report we present a 5-year old boy who was misdiagnosed to have Cerebral Palsy (CP). He struggled in maintaining his gait during the day to a degree that he was crawling in the afternoon. He was obligated to attend a school for the special need. Once the proper diagnosis of DRD was reached and treatment was initiated, he showed a dramatic improvement and was able to return back to his former school. DRD is a rare, easily missed disease which should be considered when a child presents with cerebral palsy-like patterns, walking difficulties, spasticity or dystonia, with a characteristic diurnal variation, normal brain MRI scan, and in the absence of history of perinatal asphyxia. We present this incidence to emphasize on the importance of keeping DRD within our differential diagnosis when dealing with similar cases.

INTRODUCTION

Dopa-responsive dystonia (DRD) can be defined as a group of clinically and genetically heterogeneous disorders that classically present as limb-onset, diurnally fluctuating dystonia including involuntary muscle contractions, tremors, and other uncontrolled movements. These symptoms improve with sustained use of levodopa medication, hence the name dopa-responsive dystonia [1].
The classical autosomal dominant DRD is due to mutations within the GTP cyclohydrolase 1 (*GCH1*) gene, which is the most common cause of DRD. This gene encodes a protein essential for dopamine synthesis. Autosomal recessive DRD is due to mutations either in tyrosine hydroxylase (*TH*) or in sepiapterin reductase *(SPR)* [2,3].
However, genetic heterogeneity and incomplete penetrance are quite common in DRD patients. Therefore, genetic screening may help establish the diagnosis of DRD, but a negative result would not exclude the diagnosis [4].

This heterogeneity in the conditions that underlie DRD leads frequently to its misdiagnosis, and thus delays the initiation of the correct treatment. It is important to establish a correct diagnosis at an early stage. This requires the use of the appropriate diagnostic tests, which include a levodopa trial, genetic testing (including whole-exome sequencing), cerebrospinal fluid neurotransmitter analysis, the phenylalanine loading test, and enzyme activity measurements [5].

The characteristic clinical features of DRD are childhood or adolescent onset of dystonia sometimes accompanied by mild Parkinsonism, marked diurnal fluctuations, as well as improvement with sleep or rest. However, diurnal fluctuations can arise in other neurologic disorders, and is not specific to DRD. A clear and constant response to levodopa, without motor fluctuations or dyskinesias, is the most essential factor that allows

physicians to distinguish DRD from other dystonias [6].

Apart from dystonia, on clinical examination, patients usually have brisk deep-tendon reflexes in the legs. They might also exhibit ankle clonus as well as dystonic toe extension that can be mistaken for a positive Babinski sign. Thus, DRD is commonly misdiagnosed as spastic Cerebral Palsy [7].

In this report, we present a case about a child who was initially misdiagnosed with Cerebral Palsy. Later on, a correct diagnosis of Dopa-Responsive Dystonia was reached, and the patient was treated accordingly. Clinical scenario, response of treatment and genetic study are described in details.

Case Presentation

A 5-year old boy was referred to the paediatric neurology department after he was seen by an orthopaedic surgeon, who was confused regarding the diagnosis surrounding the child's achilles tendon contracture problem.

According to his parents, the child has been diagnosed by several physicians with mild Cerebral Palsy (CP) with bilateral achilles tendon contracture, and was advised to undergo physiotherapy. The history goes back to a couple of years ago when the child began to walk; his parents noticed that in the morning his gait was normal, but later on he was struggling with his gait and fell frequently. Occasionally in the afternoons, he was totally unable to walk and only crawled. The history was clear that this child on waking up from sleep had normal gait and movement. Later on in the day, he starts having a spastic gait with tip-toe walking and clenching of the toes. The parents also noticed that when the child sleeps during the day, he becomes slightly better when he wakes up, but then later on, he starts having the same problem again. There was *NO family history* of similar conditions. The child was also obligated to attend a school for the special need due to his constant falling and inability to participate in the class.

On physical examination, the child was examined in the morning; he was able to walk steadily, but he was apparently running more on tip-toes. He was able to put his heels down and there was no obvious achilles tendon contracture. There were no other contractures in his knees or elbows. The tone felt slightly increased in the lower limbs and deep tendon reflexes were slightly increased. The child had normal cognitive function and cranial nerves. No organomegaly nor neurocutaneous stigmata were found.

The cause of dystonia may be obvious in patients with affected family members or may be strongly suspected because of some unique clinical feature. However, more often, treatment trials and observation are required to determine the cause. Additionally, imaging studies can be useful in diagnosing secondary dystonia. As treatment and also diagnostic test for DRD, the child was put on Levodopa® and Carbidopa® (25 mg, 3 times per day) and a follow-up was arranged for him after 4 weeks. Also an MRI scan was performed which showed no abnormalities (Figure 1).

On follow-up, the child showed good response to the treatment. A genetic test was requested for the GCH1 gene, which detected a homozygous variant of uncertain clinical significance in exon 1 of the GCH1 gene c.175C>G (p.Arg59Gly). To date, this variant is not described in the 1000 Genomes or the Exome Sequencing Project. However, it is reported in ExAc with a frequency of 0.00001 (i.e. in 1 among 87426 alleles).

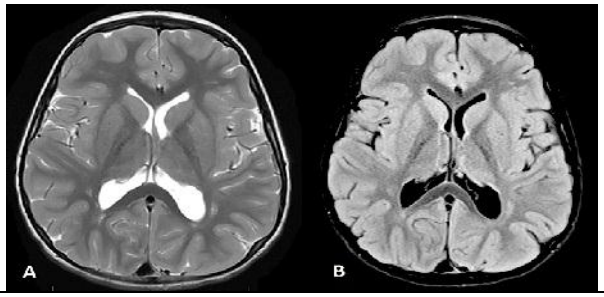
The detected variant is classified in class 3 according to CentoMD and the ACMG recommendations, which means *"Variant of Unknown Significance"* (VUS). i.e. previously reported as a VUS, or previously unreported and may or may not be the cause of the disorder.

This variant has been previously reported in the study by Kim et al., 2008. They detected it in a patient with mild symptoms of DRD, with negative family history of this disorder, along with another pathogenic mutation R198W. They concluded that this variant, c.175C>G (p. Arg59Gly), caused modestly decreased expression of R198W mutant allele and thus leading to the predisposition of a genetic disease in susceptible individuals [8].

These results suggest that a diagnosis of DRD was possible but cannot be finally confirmed.

In the succeeding meeting, the child was much more active and appeared to be responding well to the treatment. A final diagnosis of DRD was made and the child was maintained on Levodopa® and Carbidopa® (25 mg 3 times per day).

Figure 1. Magnetic Resonance Images of the child's brain; axial view T2 WI (A), and Flair axial view (B); showing normal basal ganglia, white matter maturation, and normal brain cortex, and cerebral ventricles. There is no evidence of brain atrophy or hypoxia.



DISCUSSION

Dopa-responsive dystonia was first described in 1976 by Segawa. There have been numerous reports ever since concerning DRD misdiagnosis as Cerebral Palsy (CP). One report in 2004 presented five consecutive children with dopa-responsive dystonia who were misdiagnosed initially with several different conditions including CP [9].

Another earlier report in 1994 also presented five patients in infancy and early childhood with various combinations of pyramidal and extrapyramidal signs. Initial impressions listed by several physicians included CP, but later on a correct diagnosis of DRD was made [10].

The oldest report we found dates back to 1989, in which Drs Kathryn Boyd and Victor Patterson discussed several DRD patients who were misdiagnosed in having CP [11].

In all these reports, they stressed on the importance of having DRD within the differential diagnosis when dealing with such cases. In this report, we present yet again another DRD misdiagnosis with CP. Unfortunately, the correct diagnosis was not recognized till after a couple of years, during which the child had to attend a school for the special need. However, with the correct diagnosis of DRD and Levodopa treatment, the child was able to return back to his former school and he is now showing good academic performance.

CONCLUSION

DRD is a rare, easily missed diagnosis which should be considered when a child presents with cerebral palsy-like patterns, walking difficulties, spasticity or dystonia, with normal MRI brain scan and no perinatal asphyxia, especially if he also presents with diurnal variation. If DRD is suspected, then a simple diagnostic test can be done by administering Levodopa. Early diagnosis of such cases can be life changing. The continued occurrence of DRD misdiagnosis cases, signifies the importance of directing attention towards this topic to help avoid the repetition of these incidents again.

A correct diagnosis can dramatically change patient's life. Dopa-Responsive Dystonia (DRD) should always be within our differential diagnosis when dealing with such cases.

Consent: A written informed consent was obtained from the patient's father for publication of this case report and any accompanying images. A copy of the written consent is available for review by the authors of this article.

This study has been reviewed and approved by SKMC Institutional Review Board/Research Ethics Committee (IRB/REC) which operates according to the Good Clinical Practice (GCP) Guidelines.

Abbreviations: DRD: Dopa-responsive dystonia; CP: Cerebral Palsy; MRI: Magnetic resonance imaging; GCH1 gene: GTP CycloHydrolase 1 gene; VUS: Variant of Unknown Significance

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AUTHORS' CONTRIBUTIONS:

Mr. Ghiath Ismayl reviewed the literature, set the design and wrote the first draft and the final draft. Dr. Essam A. Elgamal read the manuscript and made significant modifications in the manuscript. Dr. Omar Ismayl was the treating neurologist involved in the care of the patient. He obtained the consent, read the manuscript and made significant modifications in the manuscript. All authors read and approved the final manuscript.

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