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J Case Rep Images Pediatr 2022;4:100013Z19SM2022.
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CASE REPORT PEER REVIEWED | OPEN ACCESS

Advent of the molecular genetic testing taking a crucial role in diagnosing clinically indistinguishable rare genetic disease

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ABSTRACT

Introduction: Genetic diseases present with overlapping clinical symptomatology very often. It can misdirect the course of the diagnosis toward a misdiagnosis, if an effective diagnostic test is not available. In this modern era of molecular genetics, the whole exome sequencing (WES) test is contributing significantly to diagnose some rare genetic diseases.

Case Report: In this case report we are going to depict a clinical scenario of a patient who was initially diagnosed with Kabuki syndrome, but later was found to have congenital disorder of glycosylation (CDG) after WES was done. Even though the clinical presentation was suggestive of both these genetic diseases, WES testing was completely able to provide us with the confirmed diagnosis of CDG.

Conclusion: Undoubtedly the contribution of WES testing in the progress of precision medicine is very remarkable. Its utilization should be maximized while suspecting any rare genetic disease.

Keywords: Congenital disorder of glycosylation, Precision medicine, Whole exome sequencing

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Received: 24 July 2021
Accepted: 22 February 2022
Published: 07 March 2022

How to cite this article

Mitra S, Banikazemi M, Chopra M. Advent of the molecular genetic testing taking a crucial role in diagnosing clinically indistinguishable rare genetic disease. J Case Rep Images Pediatr 2022;4:100013Z19SM2022.

Article ID: 100013Z19SM2022

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doi: 10.5348/100013Z19SM2022CR

INTRODUCTION

The advent of the modern molecular genetic test such as the whole exome sequencing (WES) test has brought diagnostic accuracy and clarity to identify and rule out rare genetic diseases that present with remarkable clinical ambiguity [1–3]. This test has also proved its potentials to identify a misdiagnosis and project the course of diagnosis toward the definite genetic etiology [4]. Its higher diagnostic yield over the conventional genetic testing is making this test more relevant and effective for clinical diagnosis of various rare genetic conditions [5].

CASE REPORT

Now a 19-year-old adolescent male, who has been followed up in our clinic since he was a toddler, had presented at the age of two with high arched eyebrow, cleft palate, palpebral fissures, flattened nasal tip, imperforate anus, short stature and had undergone several corrective surgeries for his congenital deformities. Continued morbidity during childhood included chronic otitis leading to conductive hearing loss, elevated liver enzymes, and one episode hypoglycemia resulting in seizure.

Based on his clinical features including his facial dysmorphology (high arched eyebrow, palpebral fissures, flattened nasal tip) in association with his short stature, chronic otitis, conductive hearing loss, and the hypoglycemia leading to seizure led to diagnosis of Kabuki syndrome. Kabuki syndrome was first described in Japanese medical literature in 1981, characterized by multisystem disorders (commonly including facial features that resemble the Kabuki a theatre art form in Japan where the artists wear elaborated facial make-up to exaggerate expressions), growth delays, intellectual disability, and short stature. At the time of initial presentation, the advanced genetic testing for confirmation of this diagnosis was not available.

The molecular test now recently made available was performed to confirm the diagnosis of Kabuki syndrome, however it came negative for the genes KMT2D/MLL2 and KDM6A. This prompted evaluation looked for other rare genetic disorders.

As part of the panel of testing, WES for CDG was done as the clinical features were also somewhat suggestive of this pathology (Table 1). It showed genes defective for phosphomannomutase (PMM) enzyme, thus confirming a diagnosis of CDG, a genetic disorder with deficiency of enzymes needed for glycosylation of various proteins that ultimately causes formation of non-dysfunctional protein materials needed for numerous body functions.

DISCUSSION

Congenital disorder of glycosylation (Table 2) was first reported in the medical literature in 1980 by Dr. Jaak Jaeken and colleagues [6]. It is a broadly used term comprising of over 130 rare genetic disorder with defect in a subtle molecular process known as glycosylation. This process consists of formation of sugar chains and their attachment to the proteins and lipids, ultimately creating glycoprotein and glycolipid. These glycoprotein and glycolipid compounds perform various important functions in the body. As this process of glycosylation requires several enzymes to function, genetic defects leading to deficiency of these enzymes can significantly disrupt the process of glycosylation and give rise to various structural/physiological abnormalities [6].

Detail sequencing of a large portion of DNA can be done through WES testing. The complete set of genetic material is known as genome. The part of genome which is responsible for coding and protein synthesis is called exon. All these exons are called together as “Exome.” Whole exome sequencing testing is able to sequence and detect any defects in these exomes. Since most of the genetic mutations which lead to disease condition are present in exons, the WES testing is able to detect those, making it a very efficient method [7].

The first successful use of WES testing was to diagnose a rare form of inflammatory bowel disease in an infant [8]. In addition to diagnosing, WES testing can also find the causative mutation which can guide treatment plan, avoidance of expensive and invasive testing, and confirmed diagnoses, which are essential for eligibility for benefits and access to clinical trials [8]. A significant study has also suggested that, WES testing has increased causal variant detection and has a higher speed of diagnosis and lower cost compared with traditional diagnostic investigations in the study population, which

Table 1: Comparison of the symptoms of our patient (Kabuki syndrome vs those of CDG)

For Kabuki syndrome	For CDG
Facial dysmorphology (high arched eyebrow palpebral fissures, flattened nasal tip)	Elevated liver enzymes, history of cholecystectomy
Hypoglycemia followed by seizure	Hypoglycemia followed by seizure
Cleft palate	Cleft palate
Short stature	Short stature
Chronic otitis	
Minor intellectual disability	

Table 2: Symptomatology of congenital disorder of glycosylation

80–99% of patients	30–79% of patients	5–29% of patients
Abnormal fat tissue distribution below the skin	Abnormal pericardium morphology	Abnormal intestine morphology
High liver enzymes	Cardiomyopathy	Renal involvement
Absent/small cerebellum	Broad forehead	Peripheral neurology
Absent/small nipples	Hypoglycemia, seizure	
Decrease in size of the outer layer of the brain due to loss of brain cells	Visual problem	
Faltering weight		
Cross-eyed		
Wide-spaced nipples		

suggest that WES testing should be done early in clinical settings with similar patient populations [9].

CONCLUSION

The diagnosis of our patient was clinically suggestive of Kabuki syndrome but was exposed to not be the case by molecular genetic testing that confirmed the diagnosis of congenital disorder of glycosylation (CDG) by whole exome sequencing (WES).

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Author Contributions

Swagata Mitra – Conception of the work, Design of the work, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Maryam Banikazemi – Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Manju Chopra – Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.