



Case Report

Use of Whole Exome Sequencing in the Evaluation of Cardiac Arrest in A Critically Ill Infant

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Abstract

The utility of Whole Exome Sequencing (WES) in the evaluation of pediatric patients has become widely understood as a result of advancement of sequencing technology. However, such genetic testing has only recently been considered in critically ill patients in the neonatal or pediatric intensive care units. Herein, we discuss the case of a two-week-old infant with a prenatally diagnosed atrioventricular canal defect who presented with cardiopulmonary arrest. The patient required extracorporeal membrane oxygenation and the disease process progressed to fatal multiorgan failure. An extensive work up including whole exome sequence was unable to confirm a diagnosis yet was critical in the evaluation of her disease, which was presumed to be caused by an inborn error of metabolism and dilated cardiomyopathy. We discuss the utility and limitations of whole exome sequencing in her work up and the complexities associated with the absence of a clear diagnosis. While there are many benefits associated with advanced genetic testing, the limitations aforementioned pose a challenge that, while lofty, may be unsettling. Further research in the field of genetics and genomics will provide more sophisticated testing that can be valuable in the evaluation of critically ill patients thought to have an underlying genetic disorder.

Abbreviations: Whole exome sequencing (WES); Pediatric intensive care unit (PICU); Atrioventricular canal (AV canal); Extracorporeal membrane oxygenation (ECMO); Computerized tomography (CT); Magnetic resonance imaging (MRI); Polymerase chain reaction (PCR); Herpes simplex virus (HSV); Epstein-barr virus (EBV); Cytomegalovirus (CMV); Intravenous immunoglobulin (IVIG); Hhemosphagocytic lymphohistiocytosis (HLH); Progressive familial intrahepatic cholestasis (PFIC)

Introduction

Technological advancements have made it possible to perform whole exome sequencing to provide diagnostic information when caring for patients thought to have an undiagnosed genetic disorder. Results of testing include detection of inherited rare pathogenic variants of Mendelian disease genes as well as new mutations [1]. However, diagnostic limitations as a result of incomplete description of genes and the presence of variants of unknown significance are practical challenges associated with genetic testing. The disease detection rate estimates of WES range from approximately 6% to 57%. This variability is affected by the method

of variant classification as well as the initial symptomatology and indication for the testing [2]. In addition, ethical issues associated with counseling and caregiver perceptions of genetic testing prove a unique challenge for providers [3]. Thus, the role of Geneticists and genetic counselors in this process cannot be overstated [4].

Case Presentation

Clinical Presentation

Herein we report the case of a two-week-old full-term infant who presented to the pediatric intensive care unit from an outside hospital with cardiopulmonary arrest. The patient had a prenatal diagnosis of an isolated balanced Atrioventricular Canal (AV) defect. The family received prenatal genetic counseling and prenatal karyotype and microarray were normal. Usual prenatal labs were negative; but, hepatitis B and C serologies were unknown. The infant was born via Cesarean section and initially required brief positive pressure support, with APGARs of 6 and 8. A post-natal echocardiogram confirmed the prenatally diagnosed complete balanced AV canal defect, mild to moderate aortic regurgitation, and normal biventricular systolic function. She was evaluated by

Pediatric Genetics prior to discharge, had no dysmorphic features, and was to follow up with both Genetics and Cardiology in the outpatient clinic. The newborn screen was normal.

On the day of admission, she had reportedly been in her usual state of health until she acutely developed altered respirations and was found limp by her parent. When emergency medical personnel arrived at the home, she required respiratory support with bag valve mask ventilation. In the emergency department, she was hypotensive, hypothermic, and mottled. Intraosseous access was obtained, she was intubated, and urgently transferred to our PICU. On arrival, she was hypotensive and bradycardic with nonpalpable peripheral pulses. She required chest compressions, which was followed by transient return of spontaneous circulation. She required fluid resuscitation, atropine, epinephrine, stress dosing of steroids, and vasopressors. There was a second cardiac arrest, and she was emergently cannulated onto extracorporeal membrane oxygenation. She was started on Cefotaxime, Ampicillin, Vancomycin, and Acyclovir empirically for treatment of clinical sepsis.

Laboratory Studies

Initial labs revealed significant lactic acidosis (pH 6.66, base deficit -29, CO₂ 69, lactate 14.9). A complete blood count revealed leukocytosis (white blood cell count 18, 200) and thrombocytopenia (platelet count of 13,000) without anemia (hemoglobin 13.9, hematocrit 41, mean corpuscular volume 118). An initial complete metabolic panel was notable for severe hypoglycemia (less than 20), hyperkalemia (6.2), acute kidney injury (BUN 24, Creatinine 1), mild hypocalcemia (ionized calcium 1.13), and evidence of liver failure (AST 215, ALT 115, total bilirubin 3.7, albumin 1.6) with associated coagulopathy (INR 9.2, PT 78.2, PTT 106, and fibrinogen 68). Urine toxicology studies were positive for barbiturates, in the setting of administration of sedative medications. Laboratory studies were obtained prior to initiation of ECMO and frequently monitored while the patient remained on the ECMO circuit.

Imaging and Diagnostic Testing

Initial imaging included a CT scan of the head, chest, and abdomen, which showed subdural hematoma, subarachnoid hemorrhage, and possible ischemic injury as well as opacification of the lungs, pericardial effusion, cardiomegaly, and left pleural effusion without evidence of hemorrhage. Due to seizure-like activity during cannulation for ECMO, she was treated with antiepileptic medications. An electroencephalogram reported excessive discontinuity for age and diffuse suppression which may be seen in cases of hypoxic/ischemic encephalopathy, sedative medication use or toxic or metabolic disturbances. An echocardiogram on admission showed altered function consistent with severe acidosis, but when repeated, revealed normal

ventricular function. A liver ultrasound was grossly normal.

Case Resolution

Consulting teams included genetics, gastroenterology, cardiology, infectious diseases, and hematology. The patient was initially treated for presumed meningitis and later treated for enterococcus faecalis bacteremia, stenotrophomonas tracheitis, and acinetobacter pneumonia. Initial blood and urine cultures obtained on admission, respiratory viral panel, HSV, EBV, CMV, hepatitis, and parvovirus serologies returned negative. The family ultimately decided to withdraw care.

Differential Diagnosis

Liver failure with associated coagulopathy and hyperammonemia suggested a possible underlying inborn error of metabolism or liver disease—primarily fatty acid oxidation disorders, tyrosinemia, mitochondrial disease, and alpha-1 antitrypsin deficiency. Severe infection, toxic ingestion, and non-accidental trauma were also considered. The most likely infectious causes included *E. coli*, Group B streptococcus, listeria, enterovirus and Herpes Simplex virus.

Genetic Testing

Urine organic acids revealed metabolites consistent with liver immaturity or metabolic liver disease, without metabolites to suggest a mitochondrial disorder. Urine succinyl acetone was negative, thus excluding hepatorenal tyrosinemia. Plasma amino acid evaluation did not suggest any specific inborn error of metabolism. Evaluation for alpha-1-antitrypsin deficiency returned negative. She was treated with intravenous immunoglobulin and dexamethasone for presumed Hemophagocytic Lymphohistiocytosis (HLH), although HLH and direct antibody testing for hemolysis later resulted negative. Neonatal hemochromatosis was also considered, but the definitive diagnosis was unable to be made while she remained on ECMO. Chromosomal breakage study was obtained to evaluate for Fanconi anemia and was normal. A repeat newborn screen revealed low T4 (1.94) with normal TSH in setting of ECMO cannulation. The carnitine level was low (6) in setting of receiving parenteral nutrition.

Whole exome sequencing was recommended given progression and severity of the patient's illness and the lack of a diagnosis despite extensive genetic work up. The family was counseled regarding the indication, potential benefits, and expected results of testing, including the possibility that there may not be a clear diagnosis. Other limitations of the testing that were discussed included cost and the time frame of analysis. The family was made aware that management of the patient's care would proceed based on the patient's clinical course and would not be affected by the presence or absence of genetic testing results. The parents agreed to proceed with whole exome sequencing of the patient's genes,

but declined testing of their own blood. They declined the option of a metabolic autopsy.

Results of the WES were obtained months after the patient's death. Findings revealed "no pathogenic variants that clearly provide an explanation for the individual's condition." Potential diagnoses suggested by the testing included congenital disorders of glycosylation, HLH, alpha 1 antitrypsin deficiency, and Progressive Familial Intrahepatic Cholestasis (PFIC) which were considered during the initial evaluation. While all of these disorders can cause severe, progressive coagulopathy, evaluation and interpretation of laboratory results were impacted by the need for systemic anticoagulation and need for multiple blood products while on ECMO. Specific genetic testing for PFIC and congenital glycosylation disorders were not performed.

Discussion

The utility of WES has been primarily studied in the evaluation of relatively stable pediatric patients. Only recently have studies, including one by Meng et al. begun to shed light on the importance of considering WES in the evaluation of critically ill patients. This large-scale retrospective study evaluated the use of WES in patients in neonatal and pediatric intensive care units and found that the results impacted the medical management of 52% of the 36% of patients whose WES testing resulted in a definitive clinical diagnosis. Similarly, Rohanizadegan et al. [5] reported the case of a critically ill patient who presented with fetal hydrops, hepatosplenomegaly, liver failure, pancytopenia, and was ultimately diagnosed with Niemann-Pick disease. Although the patient was initially to undergo evaluation for a liver transplant, once the diagnosis was confirmed, the decision was made to pursue palliative care. In this particular case, the diagnosis and knowledge of prognosis significantly altered the patient's management.

The case at hand presents a diagnostic dilemma in which a previously asymptomatic patient with a known cardiac defect presents with cardiorespiratory failure with neither clear etiology nor well understood precipitating event. During the hospitalization, she received ECMO support and progressed in her multiorgan failure. The family opted to pursue WES as part of her genetic work up; yet, the definitive diagnosis was undetermined. The presumed diagnoses were an inborn error of metabolism and dilated cardiomyopathy.

Studies of clinical genome and exome sequencing have found that gene testing is often successful at providing results that are relevant for the patients and for their family members. The detection rates of WES (approximately 6%- 57%; [2]) are estimated to be higher than those of chromosomal microarray (15%-20%; [1], chromosomal studies (5%-10%; [1], and other similar genetic tests. Detection of a pathogenic variant and knowledge of potential implications for the family can be both diagnostic and reassuring.

However, identifying a pathogenic variant may not always clearly delineate the expected disease course or treatment outcomes as WES is unable to detect chromosomal abnormalities detected by microarray or karyotype [2].

Genetic testing can also detect variants of uncertain significance, which may also be unsettling for some families, particularly in cases where the disease-causing variant is not detected. In other cases, limited health literacy may also impact the family's understanding of the results. As such, genetic counseling plays a pivotal role in assessing the family's understanding of not only benefits and limitations of testing, but also their understanding of test results and their implications. We acknowledge the importance of the continuously evolving knowledge of genetic variants and their role in potentially truncating the diagnostic odyssey that many families face [1]. In cases where this dilemma persists, it is the responsibility of the healthcare team to utilize a multispecialty and multidisciplinary approach to ensure that all aspects of the patient's care are optimized.

Financial Disclosure

The authors have no financial relationships relevant to this article to disclose.

Potential Conflicts of Interest

The authors have no conflicts of interest to disclose.

Contributors' Statement Page

Dr. Lanlokun was involved in the patient's care from initial presentation to the pediatric intensive care unit, drafted the initial manuscript and revised it.

Dr. Holloway was also involved in the patient's care from initial presentation to the pediatric intensive care unit and revised the manuscript.

Dr. Greene was the Geneticist who consulted on the patient upon initial presentation. She reviewed the manuscript.

Julie Frank was the Genetic counselor who reviewed the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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