Case Report

A Case of Consanguinity

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Abstract
A newborn of unknown gestational age and unknown chronological age was admitted to the neonatal intensive care unit after presenting to the emergency department for evaluation and concern for neglect. The infant was found at home by authorities with no adult caretaker. As part of routine newborn care, this infant was noted to have an abnormal newborn metabolic screen. Subsequent genetic testing confirmed an inborn error of metabolism. When family and social history became available, it was determined that the mother and putative father were genetically related. This case report discusses newborn metabolic screening and inborn errors of metabolism and their relationship to consanguinity.

Keywords
consanguinity, metabolic disorder, inborn error of metabolism

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Case Presentation
BG was an estimated 39-week term newborn born via vaginal delivery at home. She presented to the Emergency Department (ED) for medical evaluation for concern for neglect by the local police department and the Department of Human Services (DHS). At the time of presentation, there were no adult family members present with the infant. The infant was suspected to have been born at home, based on a report from a sibling. Given this presentation, maternal medical history, obstetric history, prenatal history, and testing results were unknown. Per DHS, there was suspected in utero drug exposure. The time and date of birth and the gestational age were unknown. A complete blood count with differential (CBC), comprehensive metabolic panel (CMP), newborn metabolic screen, urine drug toxicology screen, and hair drug toxicology screen were obtained in the ED. CBC and CMP were unremarkable, except total bilirubin of 10.2. Urine drug toxicology screen was positive for amphetaamines and cannabinoids. Hepatitis B vaccine, vitamin K injection, and erythromycin ophthalmic ointment were administered. While in the ED, the infant had an episode of bilious emesis. The pediatric surgery service was consulted. Imaging studies performed in the ED, including an acute abdominal series and an upper gastrointestinal (GI) study, were unremarkable. A Replogle tube was placed, and the infant was admitted to the neonatal intensive care unit (NICU).

Hospital Course
On NICU admission, the infant was well-appearing and sleeping. On examination, scleral icterus was present, and a subconjunctival hemorrhage was appreciated in the right eye. Capillary refill was less than 2 seconds. The infant was ordered nothing by mouth and the Replogle tube continued with a plan to obtain serial X-rays and then perform barium enema to evaluate for Hirschsprung Disease once contrast passed through the gastrointestinal system from the upper GI study. Meconium drug toxicology screen was obtained. The infectious disease service was consulted due to unknown maternal infectious status during pregnancy and delivery. Hepatitis C antibody, rapid plasma reagin (RPR),

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and human immunodeficiency virus 1 and 2 antigen and antibody screen were obtained. These tests were non-reactive. The infant received hepatitis B immune globulin. Phototherapy was initiated due to an unknown date and time of birth. A maternal aunt visited on hospital day (HD) 2. She provided history that the mother reported the infant was born over 24 hours prior to the infant’s arrival to the ED. She also reported that the mother and putative father of this infant were half-siblings and shared the same father. Phototherapy was discontinued after this information became available as the infant was below the treatment threshold.

On HD 4, the infant’s X-ray continued to show contrast from the previous imaging study. The pediatric radiologist was consulted to determine if barium enema could be performed. With the infant now passing stool, it was recommended to start small enteral feeds while monitoring feeding tolerance. She tolerated enteral feeding advancement to goal feeding volumes without incident.

During the NICU hospitalization, the state newborn metabolic screen resulted as abnormal for organic acids with elevated C5-OH level of 4.8 μmol/L (normal <0.6 μmol/L), C5-OH/C8 level of 98.4 μmol/L (normal <10 μmol/L), and C5-OH/C0 level of 0.22 μmol/L (normal <0.02 μmol/L). The Department of Health recommended obtaining a plasma acylcarnitine level, urine organic acid levels, and monitoring daily basic metabolic panel and ammonia. The ammonia level was slightly elevated (92 μmol/L, normal 55-90 μmol/L) on initial check; repeat level was normal. Urine organic acids showed elevated methylcrotonylglycine. Genetics was consulted due to the abnormal newborn metabolic screen. Recommendations included genetic testing, carnitine level, and frequent feeding. The carnitine level was low; therefore, genetics recommended starting levocarnitine and outpatient genetics follow up.

An echocardiogram was obtained due to a murmur. The echocardiogram was significant for a thickened and doming pulmonary valve with mild pulmonary valve stenosis. A very small secundum atrial septal defect was identified. The pediatric cardiology service was consulted and recommended outpatient cardiology follow up 6 months after discharge.

Hair drug toxicology testing confirmed the presence of methamphetamine with a lesser amount of amphetamine and tetrahydrocannabinol (THC). Urine confirmation by mass spectroscopy confirmed the presence of methamphetamine and amphetamine. Meconium drug testing confirmed positive results of methamphetamine and THC.

Discussion

Although uncommon in the western world, consanguinity is present in up to 10% of the world’s population. It is well known that a history of consanguinity can increase the risk of inborn errors of metabolism. Congenital defects and disorders can be up to 2.5 times higher in children of consanguineous parents than unrelated parents. It is thought that the lack of genetic variation increases the probability of recessive genes being expressed. First cousins are usually the most common consanguineous relationship; the closer the parents are genetically related, the higher the risk of the child expressing recessive disorders. In this case, the parents were half-siblings.

3-methylcrotonyl-CoA carboxylase deficiency (3-MCCD) is an inborn error of metabolism in which the metabolism of the amino acid leucine is affected, resulting in increased levels of various metabolites, principally C5-OH. Historically, it was only evaluated and diagnosed after clinical presentation. In recent years, it has become more prevalent following its inclusion in newborn screenings, accounting for 90% of diagnoses. Although the disorder has become more prevalent due to its addition in newborn screenings, not much is understood about its relation to consanguinity or overall genetic factors.

3-MCCD is phenotypically expressed in a spectrum of pathological findings. A majority of patients with the disorder are asymptomatic. Others may have a variety of pathologic findings including failure to thrive, seizures, and hypoglycemia. In the case of this patient, symptoms on admission included jaundice, subconjunctival hemorrhage, and heart murmur. The patient’s carnitine and C5OH levels were low; however, hypoglycemia, seizures, or other metabolic presentations were not noted. This may be due to lack of phenotypic symptoms altogether or lack of presentation due to routine screening that led to prevention, especially for hypoglycemia.

It is difficult to determine whether or not this recessive karyotype is related to consanguinity, as contact with the parents are limited. The mother lacked prenatal care and endorsed substance abuse, both of which contribute to genetic mutations in the newborn. It is currently difficult to predict the severity of symptoms or the probability of parents passing it to their children based on specific genetic mutations. These variables affect the ability to pinpoint the most likely contributor of the development of 3-MCCD or determine a patient’s risk of morbidity and mortality. The treatment team has strong suspicion that consanguinity plays a significant role in this particular case due to the abnormal lab findings and atypical symptoms.
For future cases, consideration of the risks and benefits of diagnosis and treatment in an asymptomatic newborn is warranted. In the case of this patient, unknown neonatal and maternal history, social situation, and infantile age allowed for appropriate genetic screening and treatment. The patient continues to be monitored by the genetics team outpatient.

**Final Diagnosis**

A homozygous pathogenic variant was identified on genetic testing, c.15263del (p.Cys509Serfs*14) in the MCC1 gene. This result was consistent with autosomal recessive 3-methylcrotonyl-CoA carboxylase deficiency. The infant followed up in the genetics clinic 3 weeks after hospital discharge. Carnitine level remained low on follow-up testing so the levocarnitine dose was increased.

**Conclusion**

3-methylcrotonyl-CoA carboxylase deficiency (3-MCCD) is an inborn error of metabolism in which the metabolism of the amino acid leucine is affected, resulting in increased levels of various metabolites, principally C5-OH. It is a disorder that has become more frequently diagnosed due to its inclusion in newborn screenings. Inborn errors of metabolism are more common in cases of consanguinity, a practice that is more often observed outside of the western world. This patient’s presentation was difficult to pinpoint as her medical and social history were unknown at the time. Once genetic screening was done and social history determined, appropriate treatment and monitoring were performed. Although 3-MCCD is most commonly asymptomatic, the factors affecting severity of symptomatic patients are not currently understood. It is reasonable to hypothesize that consanguinity and its relation to inborn errors of metabolism can indeed increase severity of symptoms in recessive disorders. Until more is understood, the decision to diagnose and treat this infant before severity of symptoms could be discovered is the most appropriate course of action. Future research will elucidate the impacts of consanguinity on the prevalence of recessive disorders with severe presentations to improve the quality of care for patients.

**Author Contributions**

CB and GW: contributed to the conception and design of this manuscript.
PJB, ZS, and MB: contributed to the analysis.
CB and PJB drafted the manuscript.
GW, ZS, and MB critically revised the manuscript. All authors reviewed, edited and gave final approval for submission.

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**Disclosure Statement**

This case report examines the cases of a pediatric patient treated at Arkansas Children’s Hospital, Little Rock, AR.

**Informed Consent**

Written informed consent for patient information and images to be published was provided by the patient’s legally authorized representative, as the patient is a minor.

**Ethics Approval and Informed Consent**

Written informed consent was obtained from the patient’s legal guardian for publication of this case report.

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