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Case Report

Discomfort with uncertainty: Is testing for Brugada syndrome in the neonatal period warranted?

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Abstract. Brugada syndrome (BrS) is rare genetic disorder, which manifests as syncope or sudden death caused by polymorphic ventricular tachycardia. Diagnosis is based on symptoms and characteristic electrocardiography findings. Identification of mutations in *SCN5A* support the diagnosis, but the yield is low. According to experts, BrS patients with a history of cardiac arrest should have insertion of an automatic implantable cardiac defibrillator and asymptomatic patients can be managed conservatively. Treatment challenges occur in patients with "intermediate" clinical characteristics and in populations where there is paucity of data such as with neonates and children. We discuss the case of a woman with BrS who is faced with decision challenges in the postpartum period. Should her newborn have testing? When? Will deferment of testing impose an unreasonable uncertainty due to delay of diagnosis? Or conversely, will premature workup impose an unnecessary intervention?

Keywords: Brugada syndrome, genetic testing, neonatal

1. Introduction

There are many genes encoding for the cardiac sodium, potassium, and calcium channels identified with mutations that lead to Brugada syndrome (BrS). They include *SCN5A*, *GPD1-L*, *CACNA1C*, *CACNB2B, SCN1B*, *KCNE3*, *SCN3B*, and *HCN4* [1]. Of all the genetic mutations, which may cause BrS, 20% of cases with a positive family history are caused by the *SCN5A* gene, as seen in the mother discussed in the case report below [2]. The *SCN5A* gene encodes a sodium channel, voltage gated type V alpha subunit, which conducts the depolarizing inward current [3]. In BrS there are many phenotypes for the *SCN5A* mutation, the most common being a loss-of-function which leads to the reduced sodium current through the channel provoking an arrhythmic event [3]. However, even with a positive family history of sudden death and a genetic mutation in the above mentioned genes, does not guarantee that a patient will manifest the syndrome. According to Hoogendijk et al. [2] limited twin studies have been done, with one report of identical male twins with the same mutation and only one who exhibits symptoms consistent with BrS. The syndrome typically manifests while a patient is at rest, with increased vagal activity, hyperthermia, hyperkalemia, hypercalcemia, alcohol intoxication, cocaine abuse, anesthetics like propofol, psychotropics like lithium, and antihistamines like fexofenadine [2,4]. The provoking factor then incites an

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arrhythmic event such as a polymorphic ventricular tachycardia or ventricular fibrillation, which manifests as syncope, seizures, nocturnal agonal respirations, or sudden death [4].

2. Case report

A 35-year-old Caucasian female G1P1001, presented in the post partum unit after an uneventful pregnancy and spontaneous vaginal delivery of a full term healthy female. Her medical history was significant for the diagnosis of BrS at 25 yr of age. After testing positive as a heterozygote for the *SCN5A* mutation, she had a procainamide electrocardiography (ECG) that confirmed BrS type I, with the typical ST-segment elevations in the right precordial leads. At 28 yr of age, she underwent implantable cardiac defibrillator (ICD) placement. She has never been symptomatic and denies palpitations, exercise intolerance, or syncope. She takes no medications, only vitamins. Throughout gestation, she had frequent cardiac monitoring. Prior to and during her remarkably natural short labor of only 3 h duration, she received no anesthetic agents. After delivery, she was closely monitored on the postpartum unit.

What prompted her cardiac and genetic work up, despite her lack of symptomatology, was her significant family history. Her mother succumbed to sudden cardiac death at age 42 yr. Her maternal grandmother also experienced what was believed to be sudden cardiac death at 45 yr of age. The patient has a healthy sister, aged 32 as well as a healthy father and maternal aunt. Her sister has tested negative for the *SCN5A* mutation and her maternal aunt has declined genetic and cardiac testing due to lack of symptoms. There was no history of sudden death of infants or children in the family. The patient lives in an urban area with her husband and is employed full time as an actuary. She is followed at a cardiovascular genetics program.

This first time mother shared concerns with the pediatrician about her newborn's possible diagnosis. She also expressed her desire to defer genetic testing. She plans to inform her daughter of her possible inherited BrS mutation once she is no longer a minor. At that time, she stated that she will support her daughter's decision to either undergo or defer testing. This mother also stated that if her daughter exhibits any clinical symptoms she will undergo prompt cardiac evaluation.

3. Discussion

BrS is a rare, genetic disorder that occurs predominantly in young, Asian males. Familial cases (50%) are inherited in an autosomal dominant pattern, and there is incomplete penetrance, and it rarely affects women [5]. The exact prevalence is unknown but may be estimated at 5 in 10,000 people in the Europe and the United States have the syndrome [4–6]. Of the healthy young adults and adults who experience sudden cardiac death, it is estimated that 4–12% are secondary to BrS [1]. The major gene identified with the syndrome is *SCN5A*, which codes for the alpha subunit of the cardiac sodium channel [5]. The mutation results in a loss of function that translates into faster re-polarization, reduction of action potential length, and resultant arrhythmia that can cause polymorphic ventricular tachycardia leading to ventricular fibrillation and sudden death [5]. The characteristic ECG patterns include a right bundle-branch block and ST segment elevations in the anterior precordial leads, although there can be significant variation among patients. The diagnosis is based on symptomatology and ECG findings. Syncope, seizures, nocturnal agonal respirations, aborted cardiac arrest, and death are the usual symptoms preceding diagnosis. Others with BrS have been diagnosed after routine ECG or when indicated due to a family history, as was the case with this woman [6]. BrS is associated with a significant risk for sudden death with mean age of sudden death at 41 ± 15 yr [7]. Some investigators use electro physiologic studies to determine the inducibility of arrhythmias in an effort to risk-stratify patients with BrS. However, the predictive value is controversial [7,8]. A recent multi-center European study conducted by Probst et al. [6] revealed a family history of sudden cardiac death and a drug-induced tachyarrhythmia on ECG were statistically not predictors of cardiac events. A spontaneous type I ECG and symptoms such as syncope and an aborted cardiac arrest were considered the only independent predictors of a possible fatal arrhythmic event [9]. The only proven treatment for ventricular tachycardia and fibrillation and preventing sudden death in patients with BrS is implantation of an automatic ICD. Pharmacologic therapies have not been found to reduce the occurrence of arrhythmic events [7,8]. Indications for ICD implantation are published in the report of the Second Consensus Conference on Brugada Syndrome [8]. According to the report, BrS patients with a history of cardiac arrest must be treated with an ICD [8]. Asymptomatic patients with no family history of sudden death can be managed conservatively with

close follow-up, without ICD implantation. Patients with "intermediate" clinical characteristics represent a treatment challenge [8].

Although a majority of the BrS *SCN5A* gene carriers are asymptomatic until the age of 35–50 yr, there are reports of arrhythmias in children as young as 2 d old due to BrS [6]. There are multiple reports of infants who succumb to sudden infant death syndrome who were found to be heterozygotes for a *SCN5A* mutation [10]. In children with BrS, fever was described as the most common precipitating factor for a cardiac event [6]. Also in many parts of the world, BrS is the second most common cause of death in young adults after road traffic accidents [7,11].

Parents may not want to know all possible consequences of their child's disorder. There is an inherent fear with thinking of possible negative consequences and an innate desire to protect the child from harm. Thus, a parent may not act in what the clinician believes is the child's best interest. When there is mounting evidence that a child should be treated, it behooves us to forgo the parents' wishes as a last case resort if all explanation and reasoning fail and treat the patient. However, when evidence is sparse, like in pediatric BrS, a clinician may not be comfortable making recommendations pertaining to testing, evaluation, or deferment. Because this child has a strong family history and the family has chosen to defer testing, should we strongly recommend hospital admission and cardiovascular monitoring each time she has a fever? Or, do we recommend conventional, standards of care for this child since the risk for sudden death in childhood is "minimal"? How should we define "minimal" in a child? Should the parents be trained in cardio pulmonary resuscitation?

Given that this infant has a 50% likelihood of carrying the SCN5A mutation and multiple close relatives with history of sudden cardiac death, there lies a possible predisposition to BrS. Secondary to the low prevalence of pediatric cases of BrS, there is no formal consensus in the literature for management of suspected BrS in infancy or childhood [11]. Therefore when treating a child with a suspected predisposition to BrS, a pediatric clinician has to use the adult guidelines for evaluation and management [11]. When using the adult guidelines, in order to assess if this infant is at a higher risk for the fatal arrhythmia of BrS, she must have an ECG which spontaneously produces coved ST segment elevations in the right precordial leads with an atypical right bundle branch block or exhibit symptoms [7,9]. If she were to require a drug challenge with sodium channel blockers such as procainamide or ajmaline to provoke ECG changes, as her mother, there is a minimal risk of a spontaneous cardiac event [9]. Recently, DeMarco et al. [12] published a pediatric case report of asymptomatic BrS unmasked by a fever in a child with a history of pediatric sudden death in family members. The report further suggested with a strong family history of sudden death with fever, the medical work-up should include an electrocardiogram [12]. The family discussed in the present case report has multiple family members who died a sudden death, and therefore the infant carries a risk of having an acute cardiac event.

As a pediatrician caring for her, one must be aware of the pediatric guidelines for children with arrhythmias in order to prevent a life-threatening event. There are not many long-term studies looking at the prevalence and outcomes of asymptomatic pediatric BrS. Three Japanese studies screening general population school age and adolescent children, all realized that the utility of screening for BrS in the juvenile population is of low yield, since the majority will develop the electrophysiologic changes with symptoms in late adolescence [13–15]. In a study done by Probst et al. [6] a fever was found to be the most common precipitating factor for an acute arrhythmic event. Therefore, after vaccines or with any febrile illness, the article recommends giving antipyretics to prevent a life-threatening event [6]. The only pediatric specific guidelines are in regard to physical activity and recreational sports participation based on recommendations for young patients with genetic cardiac disease [16]. Maron et al. [16] mention BrS usually is triggered by vagal stimulation and fever, and a child with the disorder may participate in recreational sports not involving strenuous activity, which may raise the core temperature above 38 °C Examples of strenuous activity includes running at a pace of 8 km per h, singles tennis, or cross-country skiing [16]. Therefore, the best recommendations the infant's pediatrician can give to the mother is how to promptly recognize the signs of fever and treat with antipyretics after vaccines or with a febrile illness.

This case illustrates various diagnostic and treatment challenges and questions the proper management in this newborn and for her family. Is a screening ECG warranted in the postpartum unit, as an outpatient, or with her first fever? Should a clinician feel comfortable respecting the mother's wishes to defer testing? When treating a patient, the process is not limited to the patient alone, but extends to the family. Thorough and repeated explanations are necessary to ensure a good understanding of the condition, as well as the degree of comfort with each outcome. The degree of discomfort also plays

an important role in decision analysis; together these factors will dictate the plan of care with a great deal of individual/family variability.

The limited data on pediatric BrS reveal the syndrome is only a small percentage of the causes of sudden cardiac death, ECG changes are prompted with fevers and usually occur in late adolescence [6,12–16]. The mother requiring a drug challenge to elicit the ECG changes of BrS, in conjunction with the available case studies and research and incomplete penetrance of the *SCN5A* gene, reassures the caring clinician that there is a minimal risk to defer genetic or ECG testing on the infant until late adolescence. As long as the pediatrician gives the mother proper anticipatory guidance regarding fever management and to engage in strenuous activity with caution, then as the caring physician, one can feel reassured that the child is receiving the proper preventive measures. Nonetheless, the worry still may linger in the mother that her daughter is at risk for a serious cardiac event in the years prior to testing. When the mother shares her concern, the clinician can provide the reassurance that her daughter is at a low risk for a BrS related life-threatening event in childhood using the above mentioned evidence. Although as the pediatrician, every time the child leaves the office after receiving vaccines, there may be a lingering fear that a post-vaccine fever could trigger an acute cardiac event.

Clinicians aim to practice evidence-based medicine and family-centered care. However, rare conditions do not allow for extensive and strongly powered research and this is often the case in pediatrics. Uncertainty is further compounded when evidence is conflicting. Tfelt-Hansen et al. [17] and other pediatric studies did not demonstrate a significant mortality risk in young children with BrS [13–15]. Therefore, should we trust that fatal consequences in children are extremely rare? Conversely, Probst et al. [6] suggest the possibility of fatal cardiac consequences with such common symptoms as fever. Therein lies our discomfort; the consuming thoughts of devastating outcomes due to our failure in giving advice or recommendations. When a parent decides to defer genetic testing, it is our duty to explain the risks, benefits, and alternatives. But what are they? Thus, in this age of gene discovery, we will be faced with many cases such as this one. As we seek to advise and educate families about uncertain outcomes, we will need to address their concerns and desires as we all navigate through our discomfort of what is unknown.

In conclusion, when treating families with rare genetic syndromes such as BrS, physicians need to employ current evidence based treatment guidelines in addition to common sense and open communication with parents and guardians to create a treatment plan, which satisfies the desires of the family while maintaining optimal care for the child. In the current case report utilizing the most recent medical evidence regarding pediatric BrS and family history, the primary care pediatrician can feel reassured there is a low probability the child will have an acute cardiac event, and therefore can support the mother in deferring a cardiac and genetics work-up until late adolescence at the child's discretion. At each visit, however, the pediatrician should provide anticipatory guidance for prompt antipyretic fever management and reassurance with the family history of adulthood BrS presentation the child has a marginal risk for an acute cardiac event within the first decade and a half of life. These measures allow a caring physician to feel consolation when treating a condition with a vast amount of uncertainty such as pediatric BrS.

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