EBioMedicine 55 (2020) 102764

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.elsevier.com/locate/ebiom

Commentary

Too much sugar leaves a sour taste: A cardiac disease caused by excess glycogen deposit

Back Sternick Eduardo

Arrhythmia and ELectrophysiology Unit, Biocor Institute, Nova Lima, Minas Gerais, Brazil

ARTICLE INFO

Article History:
Received 18 March 2020
Accepted 7 April 2020
Available online xxx

Unexplained cardiac hypertrophy is most commonly associated with hypertrophic cardiomyopathy, the number one monogenic cardiovascular disorder. Echocardiography-based epidemiological studies have shown a disease prevalence of 1 per 500 individuals, but a prevalence of 1 per 200 is estimated by clinical and genetic data including family members [1].

Hypertrophic cardiomyopathy is inherited in an autosomal dominant pattern, associated with mutations in the contractile components of the sarcomere or Z disk. A small subset with unexplained hypertrophy, however, have mutations in genes not related to the sarcomere. One of these is *PRKAG2*, which encodes the gamma2 subunit of the adenosine monophosphate activated protein kinase (AMPK) [2]. In contrast to hypertrophic cardiomyopathy, which is not characteristically a progressive disorder, PRKAG2 cardiomyopathy patients manifest progressive symptoms around the second decade of life. It is crucial to correctly differentiate those disorders because their management and prognosis are diverse.

In this issue of *EBioMedicine* Dan Hu and colleagues report on the identification, clinical manifestation and structural mechanisms of mutations in AMPK associated cardiac glycogen storage disease. They investigated 885 patients with unexplained hypertrophy and found 25 carriers (2.8%) from 12 independent families harboring 5 different variants of *PRKAG2* gene mutations. The reported incidence could be twice as high (~5%), if the 22 family members who died from cardiac disease had been included in the study population [3].

A growing body of evidence suggests that AMPK plays a role in normal renal physiology and pathogenesis of hypertension and kidney disease [4]. Hypertension has been systematically reported in patients with *PRKAG2* mutations [5]. Hu et al. reported acute glomerulonephritis in one *PRKAG2* mutation carrier who evolved to end-stage kidney disease at 26 years of age. Giudici et al. reported a 36-year old *PRKAG2* mutation carrier who developed IgA glomerulonephritis and suggested a possible link with *PRKAG2* [6]. In this regard, others have identified differential expression of *PRKAG2* in cases of chronic kidney disease, suggesting that *PRKAG2* mutation carriers could have higher susceptibility to chronic kidney disease [7].

Abnormal lipid metabolism may occur with dysfunctional AMPK. Chronic AMPK activation in mice carrying γ2 mutation, induces obesity and reduces β cell function, impairing insulin secretion in a murine model of *PRKAG2* mutation. This involves augmentation of ghrelin signaling-dependent hyperphagia. Humans bearing the homologous γ2 *R302Q* mutation show key aspects of the murine phenotype, particularly increased adiposity and reduced β cell function [5].

Through computational modeling, Hu et al. highlighted the mechanistic pathogenic role of a number of residues. They found that even remote mutations on the surface of the protein (such as *N488I* and *L341S*) can lead to a disruption in the nucleotide binding pocket and decrease the binding affinity for ligands. *H401D* and *T400N*, in addition to affecting the nucleotide binding pocket, also disrupt the intersubunit interface. This would explain the dysfunctional AMPK regulation and its deleterious effect on cellular homeostasis pathways [3].

Sudden cardiac death in *PRKAG2* mutation carriers is frequent and occur early in life [8,9]. A timely pacemaker implantation will probably prevent sudden death as advanced atrioventricular block and severe sinus bradycardia is a common feature in patients already in the third decade. Another mechanism of sudden death is pre-excited atrial fibrillation and very fast ventricular rate. Ventricular pre-excitation is present in two-thirds of the most common mutation, *R302Q*, and may set the stage for fast ventricular rates. One unresolved issue is the occurrence of ventricular tachycardia and ventricular fibrillation as a mechanism of sudden death. Some patients receive an implantable cardiac defibrillator for primary prevention because of a mistaken diagnosis of hypertrophic cardiomyopathy. Most therapies were caused by episodes of fast atrial fibrillation [8]. Hu et al reported a sudden cardiac death incidence of 16.7%. However, they could not shed light on the mechanism of sudden cardiac death because they could not differentiate ventricular tachycardia from pre-excited atrial fibrillation. It seems that there is a lower risk of ventricular tachycardia in this condition. Sternick et al., reported no ventricular tachycardia induction during programmed ventricular stimulation [10]. Cardiac magnetic resonance shows late gadolinium enhancement in only one fourth of the patients [11]. Myocardial biopsy samples usually do not show fibrosis [12,13], except in patients with end-stage heart disease, like the one reported by Hu et al.

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2020.102723, http://dx.doi.org/10.1016/j.ebiom.2020.102732.
E-mail address: eduardosternick@gmail.com

https://doi.org/10.1016/j.ebiom.2020.102764

Campuzano et al. also in this issue of *EBioMedicine*, re-analysed 104 patients with inherited arrhythmogenic syndromes and 17 post-mortem cases in which inherited arrhythmogenic syndrome was the likely cause of death, and found that two thirds of the rare genetic variants previously classified as likely pathogenic, were reclassified as of unknown significance ten years later [14].

In contrast, *PRKAG2* mutations have shown complete penetrance. Hu et al reported that 22 distinct heterozygous variants of *PRKAG2* mutation have been described, all of them located close to adenosine nucleotide binding CBS domains. However, reviewing cases reported in the literature and ClinVar, we compiled 34 distinct mutations. There are 21 variants, labeled as pathogenic (n = 14), likely pathogenic (n = 6), and with conflicting interpretations of pathogenicity (n = 1) at ClinVar. We also found an additional 13 variants in the literature. However, the total number of patients does not exceed 250 worldwide (excluding an equal number of family members who died due to heart failure or sudden death). Considering the incidence of 5% of *PRKAG2* mutation carriers in those with unexplained hypertrophy and deceased family members, as found by Hu et al, a prevalence of *PRKAG2* mutation of 1 per 10,000 adult individuals can be estimated in the general population. Similar work in 84 children (<15 years of age) with unexplained hypertrophy yielded only 1 case with *PRKAG2* mutation (1%) and a sarcomeric gene mutation in 46 cases (54%) [15]. In a different cohort of 24 patients with unexplained hypertrophy and ventricular pre-excitation, one third have a *PRKAG2* mutation, and one sixth had *LAMP2* mutation, a yield of 46% for glycogen storage disease [16]. Hu and colleagues are to be commended for their contribution in increasing our understanding of the abnormal protein pathogenesis and increasing awareness of *PRKAG2* cardiomyopathy.

Declaration of Competing Interest

There is no conflict of interest to disclose

References

[1] Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. N Engl J Med 2018;379(7):655–68. doi: 10.1056/NEJMra1710575.

[2] Gollob MH, Green MS, Tang AS, et al. Identification of a gene responsible for familial Wolff-Parkinson-White syndrome. N Engl J Med 2001;344:1823–31. doi: 10.1056/NEJM200106143442403.

[3] Hu D, Hu D, Liu L, et al. Identification, clinical manifestation and structural mechanisms of mutations in AMPK associated cardiac glycogen storage disease. EBio Med 2020:52. https://doi.org/. doi: 10.1016/j.ebiom.2020.102723.

[4] Tain YL, Hsu CN. AMP-activated protein kinase as a reprogramming strategy for hypertension and kidney disease of developmental origin. Int J Mol Sci 2018;19(6):1744–57. doi: 10.3390/ijms19061744.

[5] Yavari A, Stocker CJ, Ghaffari S, et al. Chronic activation of gamma2 AMPK induces obesity and reduces beta cell function. Cell Metab 2016;23(5):821–36. doi: 10.1016/j.cmet.2016.04.003.

[6] Giudici MC, Ahmad F, Holanda DG. Patient with a PRKAG2 mutation who developed immunoglobulin a nephropathy: a case report. Eur Heart J Cas Rep 2019. doi: 10.1093/ehjcr/ytz038.

[7] Wang E, Zhao D, Du L. Functional prediction of chronic kidney disease susceptibility gene PRKAG2 by comprehensively bioinformatics analysis. Front Genet 2018;9:1–9. doi: 10.3389/fgene.2018.00573.

[8] Yavari A, Sarma D, Sternick EB. Human gamma2-AMPK mutations. Methods Mol Biol 2018;1732:581–619. doi: 10.1007/978-1-4939-7598-3_37.

[9] Albernaz-Siqueira MH, Honorato-Sampaio K, Dias GM, et al. Sudden death associated with a novel H401Q PRKAG2 mutation. Europace 2020:22. doi: 10.1093/europace/euaa014/5811872.

[10] Sternick EB, Oliva A, Gerken LM, et al. Clinical, electrocardiographic, and electrophysiologic characteristics of patients with a fasciculoventricular pathway: the role of PRKAG2 mutation. Heart Rhythm 2011;8(1):58–64. doi: 10.1016/j.hrthm.2010.09.081.

[11] Sri A, Daubeney P, Prasad S, Baksi J, Kinali M, Voges I. A case series on cardiac and skeletal involvement in two families with PRKAG2 mutations. Case Rep Pediatr 2019;2019:1–7. doi: 10.1155/2019/7640140.

[12] Arad M, Benson DW, Perez-Atayde AR, et al. Constitutively active AMP kinase mutations cause glycogen storage disease mimicking hypertrophic cardiomyopathy. J Clin Invest 2002;109(3):357–62. doi: 10.1172/JCI14571.2.

[13] Back Sternick E, de Almeida Araújo S, Ribeiro da Silva Camargos E, Brasileiro Filho G. Atrial pathology findings in a patient with PRKAG2 cardiomyopathy and persistent atrial fibrillation. Circ Arrhythm Electrophysiol 2016;9(12). doi: 10.1161/circep.116.004455.

[14] Campuzano O, Sarquella-Brugada G, Fernandez-Falgueras A. Reanalysis and reclassification of rare genetic variants associated with inherited arrhythmogenic syndromes. EBio Med 2020:52. https://doi.org/. doi: 10.1016/j.ebiom.2020.102732.

[15] Morita H, Rehm HL, Menesses A, et al. Shared genetic causes of cardiac hypertrophy in children and adults. N Engl J Med 2008;358:1899–908. doi: 10.1056/NEJMoa075463.

[16] Arad M, Maron BJ, Gorham JM, et al. Glycogen storage diseases presenting as hypertrophic cardiomyopathy. N Engl J Med 2005;352:362–72. doi: 10.1056/NEJMoa033349.