CLINICAL REPORT

AMERICAN JOURNAL OF medical genetics PART A

Is Cardiac Rhabdomyoma a Feature of Birt Hogg Dubé Syndrome?

Davide Bondavalli,[1,2,3] Susan M White,[4,5] Andrew Steer,[2,5,6] Andreas Pflaumer,[4,5,7] and Ingrid Winship[1,2]*

[1]Genetic Medicine and Family Cancer Clinic, Royal Melbourne Hospital, Melbourne, Australia

[2]Department of Medicine, Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia

[3]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics and Maternal Child Health, Section of Medical Genetics, University of Genoa, Genoa, Italy

[4]Victorian Clinical Genetics Services, Murdoch Children's Research Institute, Melbourne, Australia

[5]Department of Paediatrics, University of Melbourne, Melbourne, Australia

[6]Group A Streptococcal Research Group, Murdoch Children's Research Institute, Melbourne, Australia

[7]Department of Cardiology, The Royal Children's Hospital, Melbourne, Australia

Manuscript Received: 29 August 2014; Manuscript Accepted: 23 November 2014

We report on a child with two cardiac rhabdomyomas. Initially, a diagnosis of Tuberous Sclerosis Complex (TSC) syndrome was suspected, although this could neither be confirmed clinically nor genetically. Coincidentally, Birt Hogg Dubé syndrome (BHD) had been previously diagnosed in members of the extended family; this prompted a diagnostic re-evaluation of the child who was found to have the known family *FLCN* mutation. We recommend consideration of cardiac rhabdomyomas as part of the clinical BHD spectrum.

Key words: cancer genetics; BHD

How to Cite this Article:
Bondavalli D,White SM, Steer A, Pflaumer A, Winship I. 2015. Is cardiac rhabdomyoma a feature of birt hogg dubé syndrome?.
Am J Med Genet Part A. 9999:1–3.

INTRODUCTION

The prevalence of primary cardiac tumors is low, as estimated by autopsy studies [Uzun et al., 2007 Kohut et al., 2010]. They may be detected prenatally and in children, and about 10% are malignant. The most common primary cardiac tumors in the pediatric age group are cardiac rhabdomyomas. These are benign, usually multiple hamartomas of striated muscular fibers located within the ventricles, with intracavity extension. Complications include cardiomegaly, arrhythmias and sudden death from obstruction of blood flow [Burke and Virmani, 2008]. Spontaneous tumor regression may occur when cells cease mitotic proliferation and undergo apoptosis, with complete resolution occurring in some. Cardiac rhabdomyoma can be either sporadic or syndromic, the latter usually linked to Tuberous Sclerosis Complex (TSC) [Kaushik et al., 2012]; a pathogenic mutation in *TSC1* or *TSC2* is detected in 52–86% of patients with rhabdomyoma [Chaurasia et al., 2013].

TSC is an autosomal dominant syndrome caused by mutations in the tumor suppressor genes *TSC1* (9q34, encodes the protein hamartin) or *TSC2* (16p13.3, encodes tuberin). Hamartin heterodimerizes with Tuberin, and the complex inhibits the mTOR downstream pathway through Tuberin GTPase activity. About two thirds of patients have a de novo TSC mutation. Characteristic skin lesions (hypomelanotic macules, facial and ungual angiofibromas, shagreen patches and fibrous facial plaques), central nervous system tumors (subependymal nodules and cortical or subcortical tubers), seizures, intellectual disability, renal angiomyolipoma and cysts, ocular hamartomas and lymphangiomyomatosis are typical for TSC. The incidence of TSC is between 1/6,000 to 1/10,000, and the condition is typically highly penetrant with variable expressivity. Up to two thirds of individuals have cardiac rhabdomyoma; these are often detected prenatally and resolve spontaneously in childhood [Uzun et al., 2007].

Conflict of interest: none.

*Correspondence to:
Ingrid Winship, Royal Melbourne Hospital - Genetic Medicine, Royal Melbourne Hospital Grattan Street, Parkville Melbourne Victoria 3050, Australia.
E-mail: ingrid.winship@mh.org.au

Article first published online in Wiley Online Library (wileyonlinelibrary.com): 00 Month 2015
DOI 10.1002/ajmg.a.36917

Birt-Hogg-Dubé syndrome (BHD) is a rare autosomal dominant syndrome caused by heterozygous mutations in *FLCN*. The typical features are benign skin lesions (fibrofolliculoma, trichodiscoma and acrochordons), renal tumors and pulmonary cysts; with a high degree of intra- and inter-familiar variability. Other features have been reported in BHD patients, but it is not clear if they belong to the spectrum of clinical variability of BHD. BHD syndrome usually presents in adult life. Cardiac rhabdomyoma has been reported only once in an individual with BHD [Toro et al., 2008].

CLINICAL REPORT

We report on a 5-month-old boy, the first child born to healthy unrelated parents. He was born at term with normal growth parameters and was healthy until five months, when he had an out of hospital cardiac arrest from which he was successfully resuscitated. Echocardiogram revealed one large tumor (16×9 mm) attached to the trabeculation in the left ventricular cavity and a further large tumor (19×9 mm) at the ventricular apex. Figure 1 shows the ultrasound features of the cardiac rhabdomyoma.

Due to the risk of recurrent tachycardia he had surgical resection of both tumors, the intraventricular lesion was resected via left ventriculotomy. Histology of the tumors confirmed rhabdomyomas. The child was developmentally normal, with no seizures and normal growth, and a postoperative electrophysiology study showed no inducible tachycardia. The proband and parents were assessed for TSC, including dermatologic examination, ophthalmology and renal scans, which were all normal. Brain MRI in the child showed a single subependymal nodule aligning the lateral border of the anterior body of the lateral ventricle. His mother had flesh colored facial papules, but histological examination of one papule was inconclusive. DNA was extracted from peripheral blood of the proband for Sanger sequencing of *TSC1* and *TSC2*; no mutation was detected.

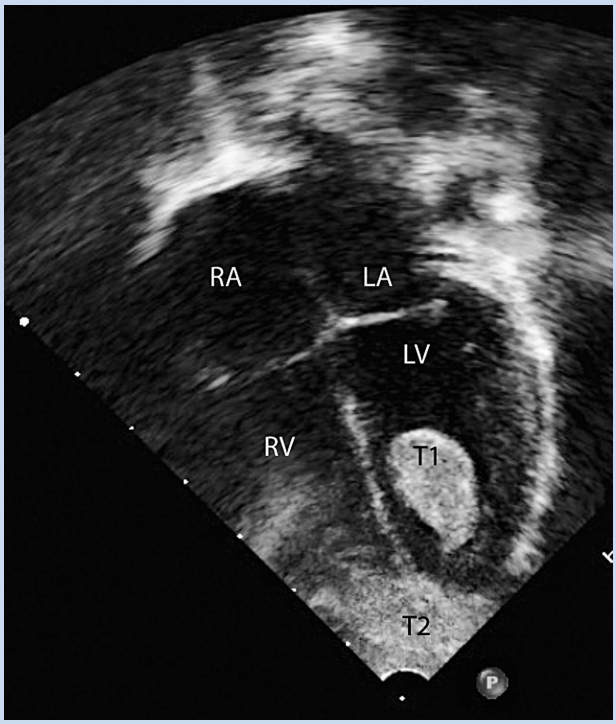

Fig. 1. Apical 4 chamber view echocardiogram: T1 is the intracardiac tumor, T2 is the epicardial tumor at the apex of left and right ventricles.

At the same time, at a family reunion interstate, the maternal grandmother discovered that relatives had been diagnosed with BHD. Despite good general health, she consented to *FLCN* testing and the familial mutation was detected. After counselling regarding the implications of further testing, including that the child was under medical surveillance for possible complications of TSC, the proband and his mother proceeded with testing and were found to carry this *FLCN* mutation c.469_471delTTC (p.Phe157del)(previously designated c.924_926delTTC). This pathogenic mutation is listed on the LOVD database and reported in the literature [Ren et al., 2008; Byrne et al., 2012; Shvartsbeyn et al., 2012; Houweling et al., 1912-1919] in patients with familial spontaneous pneumothorax and with BHD. Of the 16 people reported in the literature as carriers of this mutation, twelve developed pneumothorax or lung cysts at the average age of 42.5 years (range 24–70 years) and three had hamartomatous skin lesions in the third decade. None developed renal cell carcinoma or other cancer.

On review, the proband's mother and maternal grandmother disclosed a long history of flesh colored facial papules. These lesions were clinically consistent with fibrofolliculoma. The mother had no other health issues at age 32 years. While the nuclear family history was not suggestive of BHD, two individuals in the extended family with the *FLCN* mutation had a chromophobe renal cell cancer at 62 years, and a pneumothorax in the fourth decade, respectively.

DISCUSSION

BHD is a rare autosomal dominant syndrome caused by mutation in *FLCN*. There is a high degree of inter- and intra-familiar variability. The typical skin lesions include fibrofolliculomas, trichodischomas and acrochordons which may increase in number and size with time, but are usually benign and rarely treated unless for cosmetic purposes. Lung cysts may be detected. Cysts may rupture spontaneously, causing pneumothorax, so that depressurised activities like scuba diving and parachuting should be avoided. Individuals with BHD are at increased risk for benign and malignant renal tumors; oncocytoma, hybrid and chromophobe renal cell carcinoma after the second decade [Khoo et al., 2003].

A report of cardiac rhabdomyoma in BHD is included in a series by Toro et al. [2008]. While cardiac rhabdomyoma is a typical manifestation of TSC, it has not been linked to other syndromes. We consider this second report of a cardiac rhabdomyoma in BHD patient clinically significant. Kotulska et al. [2009] found that the mTOR pathway is involved in the pathogenesis of cardiac rhabdomyoma in TSC, demonstrating the involvement of *TSC1* and *TSC2*. Likewise, *FLCN* is involved in the mTOR pathway, providing a possible explanation for cardiac rhabdomyoma in BHD. Furthermore, Kouchi et al. [2006] report cardiac rhabdomyoma in 15 of 125 heterozygote Nihon rats, which are Sprague–Dawley rats that harbour heterozygous mutations in *Bhd*, thereby supporting con-

sideration of the cardiac tumor as a potential syndromic feature of BHD. Additional support for the overlap between BHD and TSC is presented by [Misago and Narisawa, 2009] who reported a facial fibrofolliculoma, the typical skin lesion of BHD, in a person diagnosed with TSC with multiple angiofibromata.

Little is known about the pediatric manifestations of BHD. While cascade predictive testing in adults is the standard of care, it is unusual to perform predictive testing for BHD in children. In this family, the implications of diagnosing BHD in childhood were raised with the parents, but they felt that diagnostic certainty and the advantage of ceasing the medical surveillance for complications of TSC were more important.

In presenting the second report of cardiac rhabdomyoma in molecularly confirmed BHD, we recommend consideration of BHD in the differential diagnosis of cardiac rhabdomyoma. A more difficult question is the implication for families with BHD. With only two cases reported, we do not believe this is sufficient evidence to recommend routine screening for cardiac rhabdomyoma in offspring of affected individuals in the absence of cardiac symptoms. While arrhythmias occur in 20–25% of tumors, sudden death is a rare complication of cardiac rhabdomyoma [Miyake et al., 2011] and so the likelihood of our patient's dramatic presentation should be low in other at-risk individuals. We wish to raise awareness among pediatric cardiologists, as well as cancer geneticists, so that the likelihood of this association may be further explored, in order to best manage the potential risks of BHD and its overlap with Tuberous Sclerosis Complex.

REFERENCES

Burke A, Virmani R. 2008. Paediatric heart tumours. Cardiovasc Pathol 17:193–198.

Byrne M, Mallipeddi R, Pichert G, Whittaker S. 2012. Birt–Hogg–Dubé syndrome with a renal angiomyolipoma: Further evidence of a relationship between Birt–Hogg–Dubé syndrome and tuberous sclerosis complex. Australas J Dermatol 53:151–154.

Chaurasia AK, Harikrishnan S, Bijulal S, Choudhary D, Tharakan J. 2013. Cardiac rhabdomyoma in familial tuberous sclerosis. J Cardiovasc Thorac Res 5:71–72.

Houweling AC, Gijezen LM, Jonker MA, van Doorn MB, Oldenburg RA, van Spaendonck-Zwarts KY, Leter EM, van Os TA, van Grieken NC, Jaspars EH, de Jong MM, Bongers EM, Johannesma PC, Postmus PE, van Moorselaar RJ, van Waesberghe JH, Starink TM, van Steensel MA, Gille JJ, Menko FH. 2011. Renal cancer and pneumothorax risk in Birt–Hogg–Dubé syndrome; an analysis of 115 FLCN mutation carriers from 35 BHD families. Br J Cancer 105:1912–1919.

Kaushik SK, Bhargava K, Kaushik A. 2012. Cardiac rhabdomyoma with LVOT obstruction and anorectal malformation in a neonate: A rare association. Indian Heart J 64:508–510.

Kohut J, Krzystolik-Ładzińska J, Szydłowski L, Smoleńska-Petelenz J, Giec-Fuglewicz G, Pajak J. 2010. The diagnosis, clinical course and follow-up of children with cardiac tumours—A single-centre experience. Kardiol Pol 68:304–309.

Khoo SK, Giraud S, Kahnoski K, Chen J, Motorna O, Nickolov R, Binet O, Lambert D, Friedel J, Lévy R, Ferlicot S, Wolkenstein P, Hammel P, Bergerheim U, Hedblad MA, Bradley M, Teh BT, Nordenskjöld M, Richard S. 2003. Clinical and genetic studies of Birt-Hogg-Dubé syndrome. J Med Genet 40:150.

Kotulska K, Larysz-Brysz M, Grajkowska W, Jóźwiak J, Włodarski P, Sahin M, Lewin-Kowalik J, Domańska-Pakieła D, Jóźwiak S. 2009. Cardiac rhabdomyomas in tuberous sclerosis complex show apoptosis regulation and mTOR pathway abnormalities. Pediatr Dev Pathol 12:89–95.

Kouchi M, Okimoto K, Matsumoto I, Tanaka K, Yasuba M, Hino O. 2006. Natural history of the Nihon (*Bhd* gene mutant) rat, a novel model for human Birt-Hogg-Dubé syndrome. Virchows Arch 448:463–471.

Misago N, Narisawa Y. 2009. Fibrofolliculoma in a patient with tuberous sclerosis complex. Clin Exp Dermatol 34:892–894.

Miyake CY, Del Nido PJ, Alexander ME, Cecchin F, Berul CI, Triedman JK, Geva T, Walsh EP. 2011. Cardiac tumors and associated arrhythmias in pediatric patients, with observations on surgical therapy for ventricular tachycardia. J Am Coll Cardiol 58:1903–1909.

Ren H-Z, Zhu C-C, Yang C. 2008. Mutation analysis of the *FLCN* gene in Chinese patients with sporadic and familial isolated primary spontaneous pneumothorax. Clin Genet 74:178–183.

Shvartsbeyn M, Mason AR, Bosenberg MW, Ko CJ. 2012. Perifollicular fibroma in Birt–Hogg–Dubé syndrome: An association revisited. J Cutan Pathol 39:675–679.

Toro JR, Wei M-H, Glenn GM, Weinreich M, Toure O, Vocke C, Turner M, Choyke P, Merino MJ, Pinto PA, Steinberg SM, Schmidt LS, Linehan WM. 2008. BHD mutations, clinical and molecular genetic investigations of Birt–Hogg–Dubé syndrome: A new series of 50 families and a review of published reports. J Med Genet 45:321–331.

Uzun O, Wilson DG, Vujanic GM, Parsons JM, De Giovanni JV. 2007. Cardiac tumours in children. Orphanet J Rare Dis 2:11.