# Hypertrophic Cardiomyopathy In A Patient With Craniofacial Syndrom: New Cardiocranial Syndrome?

V Kalra, F Kiblawi

## Citation

V Kalra, F Kiblawi. *Hypertrophic Cardiomyopathy In A Patient With Craniofacial Syndrom: New Cardiocranial Syndrome?*. The Internet Journal of Pediatrics and Neonatology. 2010 Volume 13 Number 1.

## Abstract

We report a 6 year follow up on a patient with a non contributory family history having constellation of anomalies comprising of HOCM, turrencephaly, foreshortened mid face with retrusion of mid facial segment, low set ears, V pattern left exotropia, nystagmus with no developmental delay. DNA analysis of this patient was negative for Pfieffer, Crouzon or Apert syndrome. Review of literature uncovered no similar case reported. We think that this patient represents a new Cardio cranial dysostosis syndrome.

# INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is a clinically heterogeneous and relatively common, autosomal dominant genetic heart disease characterized morphologically by marked hypertrophy of the left ventricle in the absence of another systemic or cardiac disease capable of causing the degree of left ventricular hypertrophy. It is the most common cause of sudden cardiac death under 35 years of age. HCM is inherited as an autosomal dominant mutation in genes that encode protein constituents of the sarcomere. HCM may occur in isolation or as a part of multisystem hereditary disorders including LEOPARD syndrome, Type II Glycogen storage disease, Sengers syndrome (Cataract, Mitochondrial myopathy, HCM).<sup>(1)</sup>

Craniosynostosis are an etiologically and pathogenetically heterogeneous group of disorders which involve premature closure of cranial sutures. Craniosynostosis may occur in syndromic or nonsyndromic forms. (2)

The association of craniosynostosis, mid face hypoplasia and hypertrophic obstructive cardiomyopathy (HOCM) has never been cited in literature. We report on a patient with unique combination of Craniofacial and hypertrophic cardiomyopathy with normal development.

# **CLINICAL REPORT**

The propositus was the product of second pregnancy of healthy non consanguineous parents; pregnancy was uncomplicated with no exposure to teratogens, smoking or alcohol. The baby was born via normal spontaneous vaginal delivery at 41 weeks of gestation with a birth weight of 8lbs 10oz and length of 21 inches. She had neonatal jaundice requiring phototherapy for 2-3 days, and no other peri-natal complications. The baby had recurrent upper respiratory tract and eye infections since birth. At 6 months of age, and while being evaluated for abnormal shape of the skull, a cardiac murmur and a gallop rhythm were detected at the pediatrician's office which led to a cardiac evaluation. Other than intermittent symptoms of upper respiratory tract infections, she was fairly asymptomatic with no history of failure to thrive, diaphoresis, tachypnea or chronic cough. She had a healthy 9 year-old sister and her family history was non-contributory. There was no family history of cardiomyopathy or sudden death.

On physical examination she appeared dysmorphic but in no apparent distress. Her HC was 44.25 cm (90 <sup>th</sup> centile). Her vital signs were within normal limits for her age. Examination of the head revealed a turrencephalic skull, grooving of temporal regions on the right and left side, hypertelorism, proptosis, protrusion of superior orbital bar, retrusion of nasal route, a foreshortened mid face lacking vertical height with retrusion of mid facial segment and low set ears. Fundus examination was normal with no evidence of Papilledema/ Optic atrophy. Musculoskeletal examination revealed small thumbs, no syndactyly, no broad thumbs, no spinal deformities and no other bony abnormalities. Cardiac examination revealed a quiet precordium with a gallop rhythm and a grade 2/6 ejection systolic murmur best heard over left lower sternal border. She had a normal neurological exam and developmental mile stones were appropriate for age.

Skull X-ray showed turrencephaly and harlequin orbits. Computed tomography of the head showed sphenobasal and low coronal synostosis with mild ventriculomegaly. On electrocardiogram (ECG), there was normal sinus rhythm with right axis deviation and biventricular hypertrophy. Two-dimensional echocardiography demonstrated normal segmental anatomy. There was severe asymmetric (eccentric) hypertrophy of the left ventricle mostly involving the mid and subaortic portions of ventricular septum (Figure 1 &2) with evidence of dynamic obstruction across the left ventricular cavity and outflow tract demonstrated by Doppler interrogation (Figure 3). The left ventricular free wall appeared less hypertrophied. There was a maximum instantaneous gradient of 60-70 mmHg across the mid ventricle and left ventricular outflow tract. There was systolic anterior motion (SAM) of the mitral valve. Mitral valve inflow Doppler was abnormal demonstrating reversal of the E:A ratio.

#### Figure 1



## Figure 2



#### Figure 3



DNA analysis was negative for any mutations in FGFR1 and FGFR2 genes.

The patient is being followed by Craniofacial, Neurosurgery, Ophthalmology and Pediatric Cardiology. No surgical intervention or repair has been required concerning the craniosynostosis. At 4 years of age she developed V pattern left exotropia with some nystagmus with no amblyopia, she is being managed conservatively with intermittent patching of the right eye.

From the cardiac standpoint she has remained asymptomatic and has been maintained on propranolol three times a day since diagnosis. Holter monitoring has revealed occasional isolated monomorphic premature ventricular contractions with no couplets and no runs of ventricular tachycardia. After approximately five years of follow-up, the patient continues to have the same findings on echocardiogram. Currently she is 6 years old her weight is 3 <sup>rd</sup> centile, height 25 <sup>th</sup> centile and HC is 95 <sup>th</sup> centile. Her developmental mile stones are appropriate for age and she is doing well in school and socially.

## DISCUSSION

A review of literature revealed no case reports of HOCM associated with craniosynostosis or craniofacial syndromes. With the combination of cardiac and craniofacial anomalies at first evaluation, the diagnosis of Pfeiffer type cardiocranial syndrome was considered (3) but lack of limb and genital anomalies along with her being developmentally appropriate for age made this diagnosis highly unlikely.

HCM is a primary cardiac disease occurring with a prevalence of 1 in 500 of the general population. (1) Of these cases, 60% are familial usually transmitted in autosomal

dominant trait with variable expression (4), this disorder has been linked to mutations at multiple chromosomal loci including 14q11-q12, 1q32, 15q22, 11p11. (5) Nevertheless HCM can be a component of multisystemic disorders including Noonan syndrome (short stature, hypertelorism, downward eye slant, low set posteriorly rotated ears, short webbed neck and epicanthal folds) Leopard syndrome (Multiple lentigines, cardiac anomalies, facial anomalies, sensorineural hearing loss, growth retardation), Friedrich ataxia, Barth syndrome, metabolic and mitochondrial DNA defects. Mutations in PTPN11, a gene encoding the protein tyrosine phosphatase SHP-2 located at chromosome 12q24 have been identified in patients with Noonan and Leopard syndrome (6,7). Our patient was lacking any of the above described syndromic features thus making these conditions highly unlikely. Hypertrophic cardiomyopathy can also be present in patients with cardio-facio-cutaneous-syndrome (CFC) in which the patients usually have multiple other congenital anomalies, none of which were present in our patient. (8)

Craniosynostosis syndromes previously classified on the basis of their clinical findings are now being defined at the molecular levels. In particular mutations in Fibroblast growth factors (FGFRs) have been identified in a number of craniosynostosis syndromes such as Crouzon syndrome (FGFR2,3) Apert (FGFR2) and Pfeiffer (FGFR1,2,3) syndromes. (9,10,). DNA analysis of the patient described in the vignette was negative for any such mutation.

Our patient had nearly isolated craniofacial dysmorphism and hypertrophic cardiomyopathy. The association between these two findings is not clear at this time. The fact that she has two relatively rare, seemingly unrelated problems is certainly intriguing and raises the question of a possible syndromic association.

#### References

1. Maron BJ, Towbin JA, Thiene G, et al. Contemporary definitions and classification of the cardiomyopathies : An American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006 Apr 11;113(14): 1807-16.

2. Cohen MM, Gorlin RJ, Fraser FC. 1997. Craniofacial disorders. In: Rimoin DL, editor. Principles and practice of medical genetics. New York: Churchill Livingstone. P 1121-1147.

3. Pfeiffer RA, Singer H, Zschiesche S (1987) : Sagittal craniostenosis, congenital heart disease, mental deficiency and various dysmorphies in two sibs- A "new" syndrome? Eur J. Pediatr 146:75-78.

4. Maron BJ, Nichols PF, Pickle LW, et al. 1984. Patterns of inheritance in hypertrophic cardiomyopathy: Assessment by M-mode and two dimensional echocardiography. Am J Cardiol 53: 1087-1094.

5. Seidman JG, Seidman C. 2001. The genetic basis for cardiomyopathy : from mutation identification to mechanistics paradigms. Cell 104: 557-567.

6. Digillo MC, Conte E, Sarkozy A, et al. 2002. Grouping of multiple –lentigines/ LEOPARD and Noonan syndromes on the PTPN11 gene. Am J Hum Genet 71:389-394.

7. Tartalgia M, Mehler EL, Goldberg R, et al. 2001. Mutations in PTPN11, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. Nat, Genet 29: 465-468.

8. M. Cristina Digilio, Giuseppe Pacileo, Anna Sarkozy, Giuseppe imongelli et. 2002. Familial aggregation of Genetically Heterogenous Cardiomyopathy. Birth defects Research (Part A): Clinical and Molecular Teratology 70; 95-98 (2004).

9. Bellus GA, Gaudenz K, Zackai EH, Clarke LA, Szabo J, Francomano CA, Muenke M. 1996. Identical mutations in three different fibroblast growth receptor genes in autosomal dominant craniosynostosis syndromes. Nat Genet 14: 174-76.

10. Rutland P, Pulleyn LJ, Reardon W, Baraitser M, Hayward R, Jones B, Malcolm S, Winter RM, Oldridge M, Slanley SF, Poole MD, Wilkie AOM.1995. Identical mutations in FGFR2 gene cause both Pfeiffer and Crouzon phenotypes. Nat. Genet 9:172-176.

## **Author Information**

Vaneet Kumar Kalra, MBBS Department of Pediatrics, St Joseph Children's Hospital

#### Fuad Kiblawi, M.D.

Department of Pediatrics, St Joseph Children's Hospital