Partial Trisomy 16q21-q24.3 with Novel Cardiac Manifestation of Left Ventricular Noncompaction Cardiomyopathy: A Case Report

Aradhana Dwivedi[1] Vivek Kumar[2] H. Ravi Ramamurthy[2]

[1] Department of Medical Genetics, Army Hospital (Research and Referral), New Delhi, India
[2] Department of Pediatric Cardiology, Army Hospital (Research and Referral), New Delhi, India

Address for correspondence Vivek Kumar, MD, DNB, FPC, Department of Pediatric Cardiology, Army Hospital (Research and Referral), Dhaula Kuan, Delhi Cantonment, New Delhi 110010, India (e-mail: vk3532@gmail.com).

J Pediatr Genet 2021;10:326–330.

Abstract

Partial trisomy 16q is most often a consequence of malsegregation from a balanced parental translocation involving chromosome 16q. It is characterized by nonspecific craniofacial dysmorphic features, hypotonia, developmental delay, psychomotor retardation, and systemic manifestations of cardiac defect, renal abnormalities, and lung abnormalities. The survival of these patients depends upon the extent and severity of the organs involved. The present literature was replete with cases of partial trisomy 16q having structural cardiac defects. However, in the present report we described a novel finding of myocardial disease in the form of left ventricular noncompaction (LVNC) cardiomyopathy associated with this genetic condition.

Keywords
- partial trisomy 16
- left ventricular noncompaction
- cardiomyopathy

Introduction

Trisomy 16 spectrum extends from full trisomy[1] to mosaic[2] to partial trisomy of long and short arms.[3] Full trisomy 16 always leads to first trimester spontaneous abortion; however, postnatal survival of partial trisomy 16 depends upon the severity of congenital defects. Unbalanced segregation of balanced parental translocation results in partial trisomy 16. The clinical features of partial trisomy of the long arm of chromosome 16 include low birth weight, hypotonia, failure to thrive, psychomotor retardation, microcephaly, and nonspecific craniofacial dysmorphism in the form of periorbital edema, prominent forehead, low set ears, flat nasal bridge, antimongoloid slant, micrognathia, hypertelorism, long philtrum, and cleft palate. Systemic abnormalities consist of congenital heart defects, renal abnormalities, lung abnormalities, and gall bladder agenesis.[4] Previously structural cardiac defects have been reported in partial trisomy 16. We herein described an unusual and novel finding of left ventricular noncompaction (LVNC) cardiomyopathy in a case with partial trisomy 16.

Case Report

A 22-month-old female toddler, firstborn of nonconsanguineous marriage, brought by her parents with concerns of delayed milestones and failure to thrive since early infancy. Antenatal history was unremarkable. She was born at term, with a birth weight of 1.7 kg (small for gestational age). Neonatal period was uneventful and family history was not contributory.

On examination, vital parameters including pulse, blood pressure, and SpO_2 were normal. Her height and weight were below 3rd percentile. Head circumference was below –3SD (microcephaly). She was noted to have dysmorphism in the form of high prominent forehead, periorbital edema, cleft palate (surgically corrected at 9 months of age), bitemporal narrowing, epicanthal folds, antimongoloid slant, and clinodactyly. Her development was estimated at around 14 months of age. Neurological examination revealed hypotonia with normal reflexes. Cardiovascular, respiratory, and abdominal system examinations were unremarkable. Hearing and eye evaluation did not reveal any abnormality. Hematological and biochemical parameters including thyroid function were

received
May 21, 2020
accepted
June 7, 2020
published online
September 2, 2020

Georg Thieme Verlag KG,
Rüdigerstraße 14,
70469 Stuttgart, Germany

DOI https://doi.org/10.1055/s-0040-1714362.
ISSN 2146-4596.

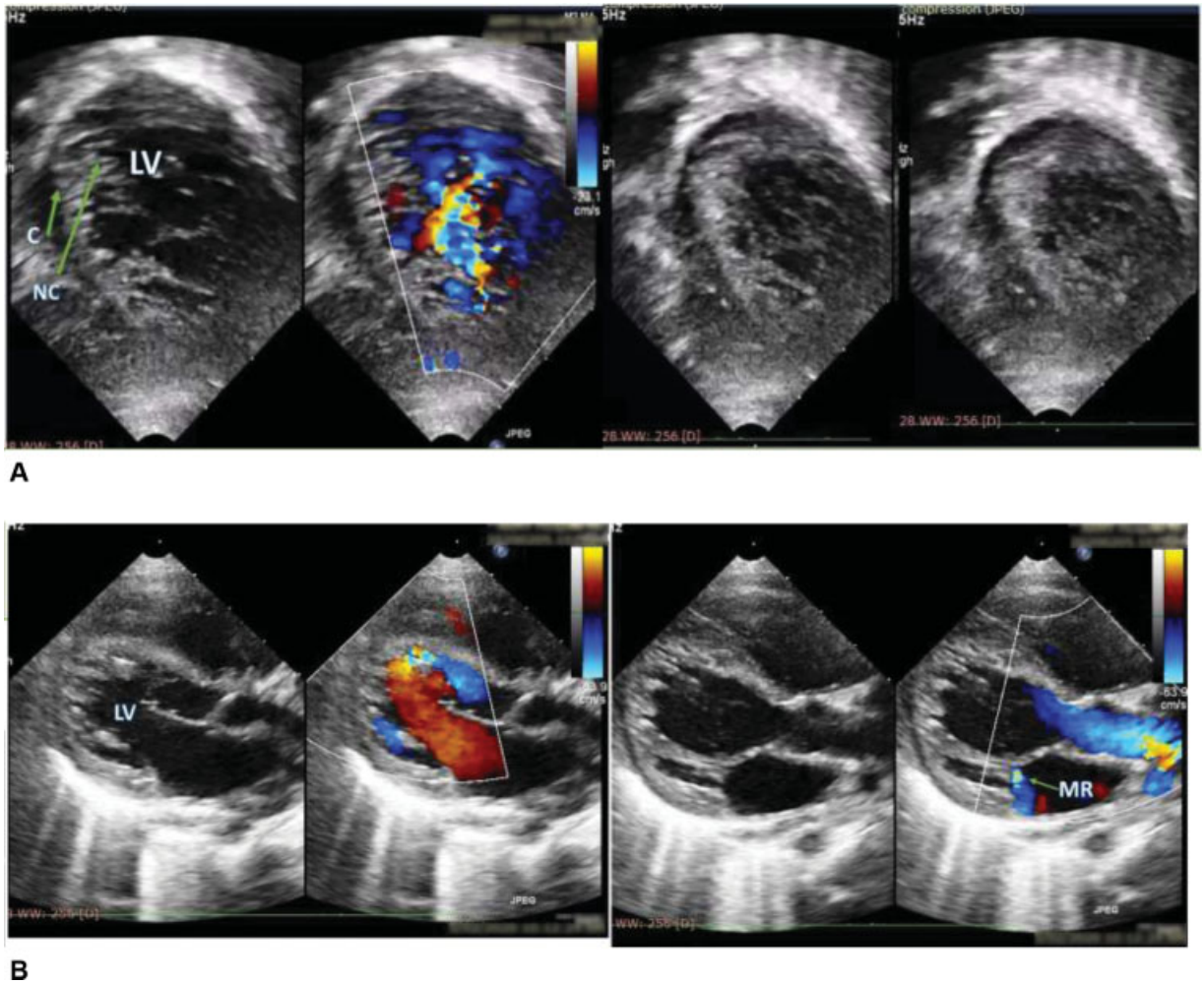

Fig. 1 Parasternal short axis view; two-dimensional (2D), color Doppler image in diastole on the left shows compacted (C) and noncompacted (NC) region **on** the septum and free wall of the left ventricle (LV) with color flow in intertrabecular recesses; two systolic frames on the right are delineating the extent of noncompacted LV. Parasternal short axis view; 2D, color Doppler image in diastole on the left and systole on the right shows apical and free wall NC of LV with mild mitral regurgitation (MR).

within normal limits. Skeletal survey and ultrasonography of the abdomen and pelvis did not show any anatomical or structural abnormality.

Echocardiography showed structurally normal heart with LVNC on the septum and on posterior and free walls in parasternal short axis. Noncompaction to compaction ratio was >2. Parasternal long-axis view showed LVNC in the apical region and posterior wall with mild mitral regurgitation. M-mode showed left ventricular (LV) ejection fraction of 63% (normal) and left ventricular internal dimension in diastole 28 mm (*z* score 1.3; LV size was normal; ►**Fig. 1A, 1B**; ►**Video 1**). Echocardiography of the parents did not reveal any abnormality.

Video 1

Parasternal short-axis view showing left ventricular noncompaction involving the septum and the free wall. Online content including video sequences viewable at: https://www.thieme-connect.com/products/ejournals/html/10.1055/s-0040-1714362.

In view of failure to thrive, developmental delay, and dysmorphism (not conforming to a single gene disorder), the presence of unbalanced chromosomal anomaly should be considered, and thus a chromosomal microarray (CMA) was ordered. CMA analysis showed a duplication of 30, 304 kb (~30 Mb) on 16q21-qter (►**Fig. 2**), consistent with a partial trisomy 16. Maternal karyotype revealed a balanced translocation between chromosomes 4q and 16q, 46,XX,t(4;16)(q34;q21), with breakpoints at 4q34 and 16q21(►**Fig. 3**). Paternal karyotype was normal.

Discussion

Our patient with trisomy of 16q21-q24.3 had a craniofacial dysmorphism consistent with the phenotypic features of partial trisomy 16. Analysis of the published data has shown that most of the patients with partial trisomy 16 have heart defects and patients with larger trisomic segments have more incidence of congenital heart defects.[5] Common congenital heart diseases reported with partial trisomy 16 include ventricular septal defect, atrial septal defect (ASD), patent ductus arteriosus (PDA), coarctation of

Fig. 2 Chromosomal microarray karyogram showing duplication corresponding to partial trisomy 16.

aorta, and interatrial septum aneurysm[6–12] (►**Table 1**). However, Mishra et al[13] for the first time had reported a case of partial trisomy 16q21-qter with complex cardiac abnormalities that included double outlet right ventricle, PDA, ASD, pulmonary stenosis, and bilateral superior vena cava. To the best of our knowledge, this report is the first case of partial trisomy 16 with LVNC cardiomyopathy. LVNC is a genetically heterogeneous condition, caused by pathogenic variation in more than one gene (e.g., MYH7, MYBPC3). It was also reported in association with other Mendelian disorders (Noonan syndrome, Sotos syndrome, etc.) and various chromosomal disorders such as 1p36 deletion, 22q11.2 deletion, or trisomy 13. The association of a partial trisomy 16 and LVNC has not been established. LVNC is a disorder of endomyocardial morphogenesis due to the arrest of the normal compaction process of developing myocardium and is characterized by prominent trabeculations with deep intertrabecular recesses.[14,15] Though there are multiple echocardiographic indices, it is commonly diagnosed by

The following paragraph needs revision. I have no clue what the authors are trying to say. It is kind of a mess.

Jenni et al described a diagnostic criterion that states that in the absence of coexisting cardiac structural abnormality, ratio of thick noncompacted layer to thin compacted layer is ≥ 2 and perfused intertrabecular recesses are supplied by intraventricular blood on color doppler analysis.[16] Isolated LVNC with normal systolic function has the best outcome.[17] However, LVNC with congenital heart disease is associated with more extensive trabeculations, worse systolic function, and genetic abnormalities.[18] Our patient needs to be monitored for LV systolic dysfunction, thromboembolic episodes, and arrhythmias, which pose a significant risk to the health.[19]

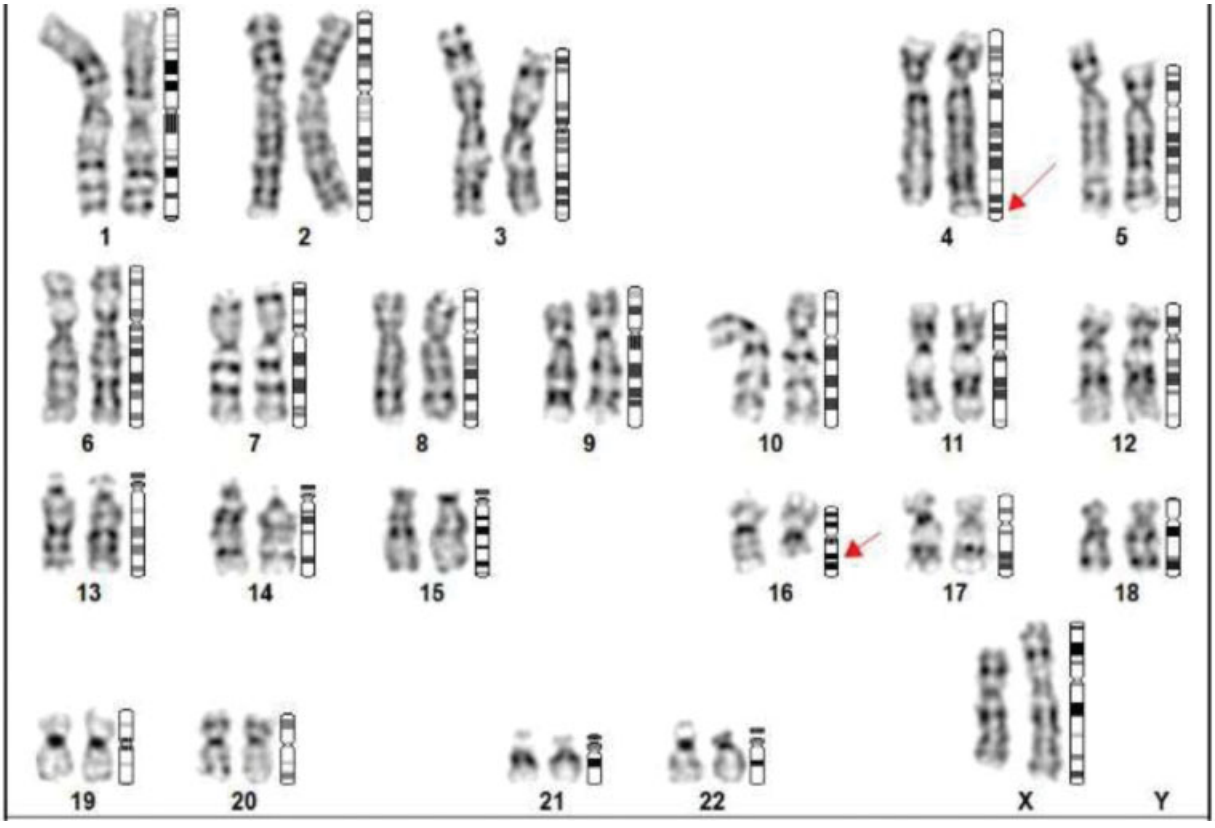

Fig. 3 Karyotype of proband's mother showing balanced translocation between the chromosomes 4 and 16, involving the regions q34 and q12.2, respectively.

Table 1 Genetic and cardiac defects of present case and comparison with previously reported cases

	Present case	Mishra et al[13]	De Carvalho et al[12]	Paladini et al[10]	Hatanaka et al[9]	Davison and Beesley[11]	Nevin et al[8]	Ridler and Mckeown[7]	Francke[6]
Trisomy	16q21-q24.3	16q21→qter	16q21→qter	16q12.1→qter	16q13→qter	16q13→ qter	16q11→qte	16q21→qter	16q?
Parental translocation	t(4;16)(q34; q12.2) mat	(15;16) (p13;q21) mat	t(4;16)(q32;q21) mat	T(16;20)(q 12.1;p13) pat	t(11;16)(q25; q13) pat	t(16;20)(q13; p13) pat	t(15;16)(p12; q11) mat	t(15;16)(p11; q11) mat	t(16q;22q) pat
Sex	Female	Female	Female	Male	Female	Female	Male	Female	Female
Cardiac defects	LVNC	DORV, VSD, PS PDA, B/L SVC	Aneurysm of interatrial septum	ASD, VSD, CoA	ASD, PDA	VSD	PDA	ASD	PDA
Survival	22 mo (Alive)	10 mo	7 y (Alive)	10 d	6 mo	5 wk	5 wk	12 d	12 mo

Abbreviations: ASD, atrial septal defect; B/L SVC, bilateral superior vena cava; CoA, coarctation of aorta; DORV, double outlet right ventricle; LVNC, left ventricle noncompaction; mat, maternal; pat, paternal; PDA, patent ductus arteriosus; PS, pulmonary stenosis; VSD, ventricular septal defect.

Conclusion

Partial trisomy 16q should be suspected in the presence of characteristics craniofacial dysmorphism, failure to thrive, developmental delay and systemic anomalies. This genetic disorder is associated with multiple structural cardiac defects. We herein reported a novel cardiac finding of LVNC cardiomyopathy in partial trisomy 16q. This isolated report does not support a causal association as LVNC has multiple etiologies. We need more reports to substantiate this connection. However, it is pertinent to monitor patients with partial trisomy 16q for the myocardial diseases besides structural heart diseases.

Funding
None.

Conflict of Interest
None declared.

Acknowledgment
The authors would like to thank the patient and her family for their help in this study.

References

1 Cusick W, Bork M, Fabri B, Benn P, Rodis JF, Buttino L Jr. Trisomy 16 fetus surviving into the second trimester. Prenat Diagn 1995;15 (11):1078–1081
2 Gilbertson NJ, Taylor JW, Kovar IZ. Mosaic trisomy 16 in a live newborn infant. Arch Dis Child 1990;65(4 Spec No): 388–389
3 Léonard C, Huret JL, Imbert MC, Lebouc Y, Selva J, Boulley AM. Trisomy 16p in a liveborn offspring due to maternal translocation t(16;21)(q11;p11) and review of the literature. Am J Med Genet 1992;43(03):621–625
4 Brisset S, Joly G, Ozilou C, et al. Molecular characterization of partial trisomy 16q24.1-qter: clinical report and review of the literature. Am J Med Genet 2002;113(04):339–345
5 Balestrazzi P, Giovannelli G, Landucci Rubini L, Dallapiccola B. Partial trisomy 16q resulting from maternal translocation. Hum Genet 1979;49(02):229–235
6 Francke U. Quinacrine mustard fluorescence of human chromosomes: characterization of unusual translocations. Am J Hum Genet 1972;24(02):189–213
7 Ridler MA, McKeown JA. Trisomy 16q arising from a maternal 15p;16q translocation. J Med Genet 1979;16(04):317–320
8 Nevin NC, Coffey WW, Nevin J, Reid MM. Partial trisomy 16q in two boys resulting from a maternal translocation, t(15;16)(p12; q11). Clin Genet 1983;24(05):375–379
9 Hatanaka K, Ozaki M, Suzuki M, Murata R, Fujita H. Trisomy 16q13−−qter in a infant from a t(11;16)(q25;q13) translocation-carrier father. Hum Genet 1984;65(03):311–315
10 Paladini D, D'Agostino A, Liguori M, et al. Prenatal findings in trisomy 16q of paternal origin. Prenat Diagn 1999;19(05):472–475
11 Davison EV, Beesley JR. Partial trisomy 16 as a result of familial 16;20 translocation. J Med Genet 1984;21(05):384–386
12 De Carvalho AF, da Silva Bellucco FT, dos Santos NP, et al. Trisomy16q21→ qter: seven-year follow-up of a girl with unusually long survival. Am J Hum Genet 2010;152:2074–2078
13 Mishra R, Paththinige CS, Sirisena ND, Nanayakkara S, Kariyawasam UGIU, Dissanayake VHW. Partial trisomy 16q21→qter due to an unbalanced segregation of a maternally inherited balanced

translocation 46,XX,t(15;16)(p13;q21): a case report and review of literature. BMC Pediatr 2018;18(01):4
14 Hayashi A, Kumada T, Nozaki F, et al. Left ventricular noncompaction cardiomyopathy in a patient with trisomy 13: a report and review of the literature. Am J Med Genet A 2017;173(07): 1947–1950
15 Weiford BC, Subbarao VD, Mulhern KM. Noncompaction of the ventricular myocardium. Circulation 2004;109(24):2965–2971
16 Jenni R, Oechslin E, Schneider J, Attenhofer Jost C, Kaufmann PA. Echocardiographic and pathoanatomical characteristics of isolated left ventricular non-compaction: a step towards classification as a distinct cardiomyopathy. Heart 2001;86(06):666–671
17 Ichida F. Left ventricular noncompaction - risk stratification and genetic consideration. J Cardiol 2020;75(01):1–9
18 Hirono K, Hata Y, Miyao N, et al; Lvnc Study Collaborators. Left ventricular noncompaction and congenital heart disease increases the risk of congestive heart failure. J Clin Med 2020;9(03):785
19 Brescia ST, Rossano JW, Pignatelli R, et al. Mortality and sudden death in pediatric left ventricular noncompaction in a tertiary referral center. Circulation 2013;127(22):2202–2208